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(54) Title: NOVEL SECRETED PROTEINS AND THEIR USES

(57) Abstract: The present invention provides nucleic acid sequences encoding novel human proteins. These novel nucleic acids are useful for constructing the claimed DNA vectors and host cells of the invention and for preparing the claimed nucleic acids, recombinant proteins and antibodies that are useful in the claimed methods and medical uses.

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NOVEL SECRETED PROTEINS AND THEIR USES

FIELD OF THE INVENTION

This application claims priority of Provisional
5 Applications Serial No. 60/224,642 filed August 11, 2000,
and Serial No. 60/241,779 filed October 19, 2000.

The present invention relates to the identification
and isolation of novel DNA, therapeutic and drug discovery
uses, and the recombinant production of novel secreted
10 polypeptides, designated herein as LP105, LP061, LP224,
LP240, LP239(a), LP243(a), LP243(b), LP253, LP218,
LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244,
LP186, LP251(b), LP255(b), and LP223(b). The present
invention also relates to vectors, host cells, and
15 antibodies directed to these polypeptides.

BACKGROUND OF THE INVENTION

Extracellular proteins play an important role in the
formation, differentiation and maintenance of multi-
20 cellular organisms. The fate of many individual cells,
e.g., proliferation, migration, differentiation, or
interaction with other cells, is typically governed by
information received from other cells and/or the immediate
environment. This information is often transmitted by
25 secreted polypeptides (for instance, mitogenic factors,
survival factors, cytotoxic factors, differentiation
factors, neuropeptides, and hormones) which are, in turn,
received and interpreted by diverse cell receptors or
membrane-bound proteins. These secreted polypeptides or
30 signaling molecules normally pass through the cellular
secretory pathway to reach their site of action in the
extracellular environment.

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Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present such as thrombolytic agents, interferons, 5 interleukins, erythropoietins, colony stimulating factors, and various other cytokines are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents.

The present invention describes the cloning and 10 characterization of novel proteins, termed LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), and LP223(b), as well as active variants and/or fragments thereof.

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SUMMARY OF THE INVENTION

The present invention provides isolated LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, 20 LP251(b), LP255(b), and LP223(b) polypeptide encoding nucleic acids and the polypeptides encoded thereby, including fragments and/or specified variants thereof. Contemplated by the present invention are LP probes, primers, recombinant vectors, host cells, transgenic 25 animals, chimeric antibodies and constructs, LP polypeptide antibodies, as well as methods of making and using them diagnostically and therapeutically as described and enabled herein.

The present invention includes isolated nucleic acid 30 molecules comprising polynucleotides that encode LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244,

LP186, LP251(b), LP255(b), and LP223(b) polypeptides as defined herein, as well as fragments and/or specified variants thereof, or isolated nucleic acid molecules that are complementary to polynucleotides that encode such LP 5 polypeptides, or fragments and/or specified variants thereof as defined herein.

A polypeptide of the present invention includes an isolated LP polypeptide comprising at least one fragment, domain, or specified variant of at least 90-100% of the 10 contiguous amino acids of at least one portion of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38.

The present invention also provides an isolated LP polypeptide as described herein, wherein the polypeptide 15 further comprises at least one specified substitution, insertion, or deletion corresponding to portions or specific residues of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38.

The present invention also provides an isolated nucleic 20 acid probe, primer, or fragment, as described herein, wherein the nucleic acid comprises a polynucleotide of at least 10 nucleotides, corresponding or complementary to at least 10 nucleotides of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37.

25 The present invention also provides compositions, including pharmaceutical compositions, comprising an LP polypeptide, an LP polypeptide-encoding polynucleotide, an LP polynucleotide, and/or an LP polypeptide antibody, wherein the composition has a measurable effect on an 30 activity associated with a particular LP polypeptide as disclosed herein. A method of treatment or prophylaxis based on an LP polypeptide associated activity as disclosed

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herein can be effected by administration of one or more of the polypeptides, nucleic acids, antibodies, vectors, host cells, transgenic cells, and/or compositions described herein to a mammal in need of such treatment or

5 prophylactic. Accordingly, the present invention also includes methods for the prophylaxis or treatment of a patho-physiological condition in which at least one cell type involved in said condition is sensitive or responsive to an LP polypeptide, LP polypeptide-encoding

10 polynucleotide, LP nucleic acid, LP polypeptide antibody, host cell, transgenic cell, and/or composition of the present invention.

The present invention also provides an article of manufacture comprising a container, holding a composition effective for treating a condition disclosed herein, and a label.

The present invention also provides a method for identifying compounds that bind an LP polypeptide, comprising:

20 a) admixing at least one isolated LP polypeptide as described herein with a test compound or composition; and

25 b) detecting at least one binding interaction between the polypeptide and the compound or composition, optionally further comprising detecting a change in biological activity, such as a reduction or increase.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Applicants have identified cDNA clones comprising polynucleotides that encode novel polypeptides or novel variants of known polypeptides:

1) LP105

LP105 polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:1 are contemplated as one embodiment of the present invention. Specifically, polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:2, as well as fragments, variants, and derivatives thereof. Accordingly, LP105 polynucleotides encoding the LP105 polypeptides of the present invention are also contemplated by the present invention. LP105 polynucleotides are predominantly expressed in prostate and kidney tissues.

The LP105 polypeptide as shown in SEQ ID NO:2 shares sequence similarity with a recently reported human Lefty protein (WO 99/09198). Lefty proteins are members of the TGF-beta family and two LEFTY genes, LEFTY A and B, have been localized by FISH to 1q42, a region syntenic to the location to which the mouse Lefty genes have been mapped at 1H5 [Kosaki, et al., *Am. J. Hum. Genet.* 64(3):712-21 (1999); Meno, et al., *Genes Cells* 2(8):513-24 (1997)]. LEFTY A is identical to EBAF [Kothapalli, et al., *J. Clin. Invest.* 99(10):2342-50 (1997)]. Analysis of 126 human cases of L-R axis malformation showed a single nonsense and a single missense mutation in the LEFTY A gene. Both mutations lay in the cysteine-knot region of the LEFTY A protein and the phenotype of affected individuals was very similar to that typically seen in Lefty-1 -/- mice with L-R axis malformations. Furthermore, the LP105 polypeptide as shown in SEQ ID NO:2 shares sequence similarity with human bone morphogenic protein 18 (WO 99/29718). Compositions comprising LP105 polypeptides, polynucleotides, and/or antibodies are useful for the treatment of defects in or

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wounds to tissues including, but not limited to, epidermis, nerve, muscle, cardiac muscle, and organs including, but not limited to liver, lung, epithelium, brain, spleen, cardiac, pancreas and kidney. Furthermore, compositions comprising 5 LP105 polypeptides, polynucleotides, and/or antibodies can be useful for modulating sexual development, pituitary hormone production, hematopoiesis, wound healing, tissue repair, and the formation of bone and cartilage. Compositions comprising LP105 polypeptides, polynucleotides, 10 and/or antibodies can also be used to treat such conditions as cancer including, but not limited to prostate and kidney cancer, interstitial lung disease, infectious diseases, autoimmune diseases, arthritis, leukemia, lymphomas, immunosuppression, immunity, humoral immunity, inflammatory 15 bowel disease, myelosuppression, periodontal disease, osteoarthritis, osteoporosis, and other abnormalities of bone, cartilage, muscle, tendon, ligament, meniscus, and/or other connective tissues as well as dysfunctional growth and differentiation patterns of cells.

20

2) **LP061**

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:3 are 25 contemplated by the present invention. Specifically, polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:4, as well as fragments, variants, and derivatives thereof. Accordingly, LP061 polynucleotides encoding LP061 polypeptides of the present 30 invention are also contemplated by the present invention. LP061 polynucleotides are predominantly expressed in diseased thyroid. The present invention includes a human

nucleotide sequence (Incyte clone 2719035H1) as shown in SEQ ID NO:3 which appears to be a shortened splice-variant of the published human fukutin nucleotide sequence (GenBank AB008226).

5 Fukuyama-type congenital muscular dystrophy (FCMD), one of the most common autosomal recessive disorders in Japan (incidence is 0.7 to 1.2 per 10,000 births), is characterized by congenital muscular dystrophy, in conjunction with brain malformation (micropolygyria). The
10 FCMD gene was mapped to a region of less than 100 kilobases which included the marker locus D9S2107 on human chromosome 9q31. The mutation responsible for FCMD is a retrotransposal insertion of tandemly repeated sequences within this candidate-gene in all FCMD chromosomes carrying the founder
15 haplotype (87%). The inserted sequence is about 3 kilobases long and is located in the 3' untranslated region of a gene encoding a new 461 amino acid protein. This novel gene, termed fukutin, is expressed in heart, brain, skeletal muscle, pancreas and lymphoblasts in normal individuals, but
20 not in FCMD patients who carry the insertion. Two independent point mutations confirm that mutation of this gene is responsible for FCMD. The predicted fukutin protein contains an amino-terminal signal sequence and one glycosylation site, which together with results from
25 transfection experiments suggests that fukutin is a secreted protein. Abnormalities in basal lamina in FCMD muscle and brain have been seen by electron microscopy [Nakano, et al., *Acta Neuropathol.* 91(3):313-21 (1996); Ishii, et al., *Neuromuscul. Disord.* 7(3):191-7 (1997)]. Therefore it has
30 been suggested that secreted fukutin may be associated with the extracellular matrix surrounding expressing cells where it forms a complex with other extracellular components to

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stabilize a microenvironment supportive for normal cellular/tissue function. In muscle, fukutin complexes might stabilize the function of muscle fibers/sarcomeres; in brain, fukutin may assist the migration of neuronal 5 precursors during cortical development [Fukuyama, et al., *Brain Dev.* 3(1):1-29 (1981)].

Accordingly, compositions comprising LP061 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of diseases, 10 disorders, and/or conditions including, but not limited to, brain malformation (micropolygria), Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, ALS, muscular pathologies including, but not limited to, muscular dystrophies including, but not limited 15 to, congenital muscular dystrophies such as fukuyama-type congenital muscular dystrophy, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, 20 paranoia, obsessive compulsive disorder, panic disorder learning disabilities, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

25 3) LP224

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:5 are contemplated by the present invention. Specifically, 30 polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:6, as well as fragments, variants, and derivatives thereof. Accordingly, LP224

polynucleotides encoding LP224 polypeptides of the present invention are also contemplated by the present invention.

The gene encoding the LP224 polypeptide has been localized to chromosome 4p16 (GenBank hit g7022852) and the 5 LP224 polypeptide as shown in SEQ ID NO:6 shares sequence similarity with a protein encoded by the leucine-rich, glioma inactivated 1 tumor suppressor gene. LGI1 has the highest homology with a number of transmembrane and extracellular proteins which function as receptors and 10 adhesion proteins. LGI1 is predominantly expressed in neural tissues, especially in brain; its expression is reduced in low grade brain tumors and it is significantly reduced or absent in malignant gliomas. Its localization to the 10q24 region, and rearrangements or inactivation in 15 malignant brain tumors, suggest that LGI1 is a candidate tumor suppressor gene involved in progression of glial tumors [Chernova, et al., *Oncogene* 17(22):2873-81 (1998)]. Accordingly, compositions comprising LP224 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, 20 treatment and intervention of bipolar affective disorder [Ewald, et al., *Mol. Psychiatry* 3(5):442-8 (1998)], hearing defects [Van Camp, et al., *J. Med. Genet.* 36(7):532-6, (1999)], cherubism [Mangion, et al., *Am. J. Hum. Genet.* 65(1):151-7 (1999)], Wolf-Hirschhorn (WH) syndrome [Zollino, 25 et al., *Am. J. Med. Genet.* 82(5):371-5 (1999); *Ann. Genet.* 41(2):73-6 (1998)], Ellis-van Creveld syndrome [EVC; Polymeropoulos, et al., *Genomics* 35(1):1-5 (1996)], autosomal dominant postaxial polydactyly, nail dystrophy, and dental abnormalities [Howard, et al., *Am. J. Hum. Genet.* 30 61(6):1405-12 (1997)], Pitt-Rogers-Danks (PRD) syndrome and overgrowth syndrome [Partington, et al., *J. Med. Genet.* 34(9):719-28 (1997)], bladder cancer and malignant brain

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tumors [Bell, et al., *Genes Chromosomes Cancer* 17(2):108-17 (1996)].

4) LP240

5 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:7 are contemplated by the present invention. Specifically, polypeptides of the present invention comprise the amino 10 acid sequence as shown in SEQ ID NO:8, as well as fragments, variants, and derivatives thereof. Accordingly, LP240 polynucleotides encoding LP240 polypeptides of the present invention are also contemplated by the present invention. The gene encoding the LP240 polypeptide as shown in SEQ ID 15 NO:8 has been localized to chromosome 19.

LP240 polynucleotides, polypeptides, and antibodies corresponding to LP240 are useful for diagnosis, treatment and intervention of diseases, disorders, and/or conditions including, but not limited to, stroke, Alzheimer's disease, 20 Parkinson's disease, Huntington's disease, neurodegenerative disorders, brain cancer, cardiovascular disease, atherosclerosis, myocardial infarction, inflammation, and rheumatoid arthritis.

25 5) LP239(a) and LP239(b)

In another embodiment, polypeptides comprising the amino acid sequences of the open reading frames encoded by the polynucleotide sequences as shown in SEQ ID NO:9 and SEQ ID NO:23 are contemplated by the present invention. 30 Specifically, LP239(a) and LP239(b) polypeptides of the present invention comprise the amino acid sequences as shown in SEQ ID NO:10 and SEQ ID NO:24, respectively, as

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well as fragments, variants, and derivatives thereof.

Accordingly, LP239(a) and LP239(b) polynucleotides comprising polynucleotides as identified in SEQ ID NO:9 and SEQ ID NO:23, respectively, are also contemplated by the

5 present invention.

LP239 polypeptide-encoding polynucleotide sequences are primarily expressed in digestive, hemic, immune, and nervous system tissues. The LP239(a) and LP239(b)

polypeptides as shown in SEQ ID NO:10 and SEQ ID NO:24

10 share sequence similarity with a thyroxine-binding globulin [see AF204929; Mori, et al., *Endocr. J.* 46(4):613-9

(1999)]. LP239 polypeptides therefore may serve as hormone binding proteins in serum, protease inhibitors, or hormones when administered to patients suffering from a deficiency

15 of endogenous LP239 polypeptides. LP239 polynucleotides, polypeptides, and antibodies corresponding to LP239 are useful for diagnosis, treatment and intervention of

diseases, disorders, and/or conditions including, but not limited to, hypothyroidism, anemia, sepsis, gram negative

20 bacteremia, allergic responses, allergic autoimmune diseases, type 1 diabetes, Th1-dependent insulitis, inflammation, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, liver failure, ARDS, cancers, leukemia, and immunodeficiency.

25

6) LP243(a) and LP243(b)

In another embodiment, polypeptides comprising the amino acid sequences of the open reading frames encoded by the polynucleotide sequences as shown in SEQ ID NO:11 and

30 SEQ ID NO:13 are contemplated by the present invention.

Specifically, LP243(a) and LP243(b) polypeptides of the present invention comprise the amino acid sequences as shown

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in SEQ ID NO:12 and SEQ ID NO:14, respectively, as well as fragments, variants, and derivatives thereof. Accordingly, LP243(a) and LP243(b) polynucleotides comprising polynucleotides as identified in SEQ ID NO:11 and SEQ ID 5 NO:13 are also contemplated by the present invention.

The gene encoding the disclosed LP243 polypeptides have been localized to chromosome 19p13.3 (GenBank hit g2894631) and is mainly expressed in nervous system and digestive system. The LP243 polypeptides as shown in SEQ ID NO:12 and 10 SEQ ID NO:14 share sequence similarity with the amino acid sequence of protein PRO227 disclosed in WO 99/14328, the amino acid sequence of the human Tango-79 protein disclosed in WO 99/06427, the glioma amplified on chromosome 1 (GAC1) protein (AF030435), and the *Rattus norvegicus* (AF133730) 15 SLIT protein. GAC1 is a member of the leucine-rich repeat superfamily on chromosome band 1q32.1. GAC1 is amplified and overexpressed in malignant gliomas [Almeida, et al., *Oncogene* 16(23):2997 (1998)]. In *Drosophila*, at least, SLIT proteins are believed to be involved in axon pathway 20 development. The two predicted proteins LP243(a) and LP243(b) as shown in SEQ ID NO:12 and 14, respectively, have different N-terminals but are identical starting from amino acid 27 through amino acid 557 as shown in SEQ ID NO:12. The present invention provides isolated LP243(a) and 25 LP243(b) polypeptides as described herein, wherein the polypeptide has at least one activity, such as, but not limited to, inducing cellular proliferation, tumorigenesis, synapse formation, neurotransmission, learning, cognition, homeostasis, neuronal outgrowth, differentiation or 30 survival, or tissue regeneration including but not limited to neural tissue regeneration. An LP243 polynucleotide,

polypeptide, and/or antibody can thus be screened for a corresponding activity according to known methods.

The present invention also provides a composition comprising an isolated LP243 nucleic acid, polypeptide, and/or antibody as described herein and a carrier or diluent. The carrier or diluent can optionally be pharmaceutically acceptable, according to known methods. LP243 polynucleotides are expressed in nervous tissues and the polypeptides encoded thereby appear to play a role in tumorigenesis, neurodegenerative diseases, behavioral disorders, and/or inflammatory conditions. Accordingly, compositions comprising LP243 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of diseases, disorders, and/or conditions including, but not limited to, cancer, including, but not limited to sporadic ovarian tumors [Wang, et al., *Br. J. Cancer* 80(1-2):70-2 (1999)], Peutz-Jeghers syndrome [Nakagawa, et al., *Hum. Genet.* 102(2):203-6 (1998); Olschwang, et al., *J. Med. Genet.* 35(1):42-4 (1998)], adenoma malignum of the uterine cervix [Lee, et al., *Cancer Res.* 15;58(6):1140-3 (1998)], pancreatic carcinomas [Hoglund, et al., *Genes Chromosomes Cancer* 21(1):8-16 (1998)], multiple myeloma and plasma cell leukemia [Taniwaki, et al., *Blood* 84(7):2283-90 (1994)], Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and

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altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

7) LP253

5 Cytokines are secreted regulatory peptides that mediate a wide range of biological activities by binding to specific cell surface receptors on target cells. Cytokine actions include control of cell proliferation and differentiation, regulation of hematopoiesis, and immune inflammatory 10 responses. Cytokines are also major orchestrators of host defense processes and, as such, are involved in responses to exogenous as well as endogenous insults and in repair or restoration of tissue integrity. In order for a cytokine to exert its effect on cells, it is now accepted by those 15 skilled in the art that the molecule must interact with molecules, located on cell membranes, referred to as receptors. Patents which exemplify disclosures of interleukin receptors include Honjo, et al., U.S. Patent 4,816,565; Urdal, et al., U.S. Patent 4,578,335; Dower, et 20 al., U.S. Patent 5,180,812; and Taniguchi, et al., U.S. Patent 5,198,359; and WO 2000/15759, the disclosures of which are incorporated by reference.

In another embodiment of the present invention, we provide polypeptides comprising the amino acid sequence of 25 the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:15. Specifically, LP253 polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:16, as well as fragments, variants, and derivatives thereof. Accordingly, 30 LP253 polynucleotides comprising polynucleotides as identified in SEQ ID NO:15 are also contemplated by the present invention. LP253 encoding polynucleotide sequences

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are primarily expressed in digestive, hemic, immune, and nervous system tissues. The LP253 polypeptide as shown in SEQ ID NO:16 shares structural similarity with other interleukin receptors.

5 The effects of IL-1 *in vivo* can be regulated via the administration of a soluble form of its receptor [Fanslow, et al., *Science* 248:739-41 (1990)]. Systemic administration of a soluble, extracellular portion of the receptor for IL-1 (soluble IL-1R) had profound inhibitory effects on the
10 development of *in vivo* alloreactivity. Survival of heterotopic heart allografts was prolonged from twelve days in controls to seventeen days in mice treated with soluble IL-1R. Lymph node hyperplasia in response to localized injection of allogeneic cells was completely blocked by
15 soluble IL-1R treatment.

The availability of the purified LP253 polypeptide, in soluble form, presents therapeutic possibilities as well. The results that Fanslow report demonstrate the ability of a soluble cytokine receptor to modulate biological activity
20 upon exogenous administration *in vivo*, presumably by acting as a neutralizing agent for the endogenously produced, corresponding ligand, and provides evidence of the therapeutic potential of soluble cytokine receptors in a variety of clinical disorders.

25 Administration of a soluble form of LP253 would interfere with the effect of its endogenous ligand on the cells, since the ligand would not bind to the endogenous membrane bound LP253 as freely. Hence, an aspect of the present invention is the treatment of pathological
30 conditions caused by excess expression and/or activity of LP253 polypeptides by adding an amount of soluble LP253 polypeptides sufficient to inhibit binding of a cytokine to

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the aforementioned cells. This methodology can also be modified, and the soluble receptor can also be used as a screening agent for pharmaceuticals. Briefly, a pharmaceutical which works as an LP253 antagonist can do so 5 by blocking the binding of endogenous ligand to the LP253. Prior to determining whether a material would be effective *in vivo*, one may use the purified LP253 polypeptide in connection with a potential pharmaceutical to determine if there is binding. If there is in fact binding, further 10 testing may be indicated.

Expression of recombinant polypeptides in high levels and its use as an antigen allows production of additional neutralizing monoclonal and polyclonal antibodies. Such neutralizing antibodies can be used in *in vivo* model 15 settings to elucidate the role that LP253 and its ligand play in normal as well as pathologic immune responses (i.e., disease states that are aggravated by activated T- and NK-cells like auto-immune diseases, graft versus host disease and rheumatoid arthritis). Thus, purified LP253 20 polypeptides, polynucleotides, and/or antibodies compositions will be useful in diagnostic assays for LP253 and its ligand, and also in raising antibodies to LP253 for use in diagnosis or therapy.

LP253 polypeptides, polynucleotides, and/or antibodies 25 can be administered, for example, for the purpose of suppressing immune responses in a human. A variety of diseases or conditions are caused by an immune response to alloantigen, including allograft rejection and graft-versus-host reaction. In alloantigen-induced immune responses, 30 soluble LP253 polypeptides may suppress lymphoproliferation and inflammation which result upon activation of T cells. Soluble LP253 polypeptides may therefore be used to

effectively suppress alloantigen-induced immune responses in the clinical treatment of, for example, rejection of allografts (such as skin, kidney, and heart transplants), and graft-versus-host reactions in patients who have 5 received bone marrow transplants.

LP253 polypeptides, polynucleotides, and/or antibodies may also be used in clinical treatment of autoimmune dysfunctions, such as rheumatoid arthritis, diabetes and multiple sclerosis, which are dependent upon the activation 10 of T cells against antigens not recognized as being indigenous to the host. LP253 polypeptides, polynucleotides, and/or antibodies may also be useful in treatment of septic shock in which interferon gamma produced in response to various interleukins plays a central role in causing 15 morbidity and mortality [Doherty, et al., *J. Immunol.* 149:1666 (1992)].

In addition, compositions comprising soluble LP253 polypeptides may be used directly in therapy to bind or scavenge endogenous LP253 ligands, thereby providing a means for regulating the immune or inflammatory 20 activities. In its use to prevent or reverse pathologic immune responses, soluble LP253 polypeptides can be combined with other cytokine antagonists such as antibodies to the other known interleukin receptors, soluble interleukin receptors, soluble TNF (tumor necrosis factor) receptors, 25 and/or interleukin receptor antagonists, and the like.

The dose ranges for the administration of the LP253 polypeptides, polynucleotides, and/or antibodies and fragments thereof may be determined by those of ordinary skill in the art without undue experimentation. In general, 30 appropriate dosages are those which are large enough to produce the desired effect, for example, blocking the binding of endogenous ligands of LP253 to endogenous LP253.

8) LP218

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the 5 polynucleotide sequence as shown in SEQ ID NO:17 are contemplated by the present invention. Specifically, LP218 polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:18, as well as fragments, variants, and derivatives thereof. Accordingly, 10 LP218 polynucleotides comprising polynucleotides as identified in SEQ ID NO:17 are also contemplated by the present invention.

The gene encoding the LP218 polypeptide as shown in SEQ ID NO:18 has been localized to chromosome 22q11 and shares 15 sequence similarity with acetyl LDL receptor. LP218 polynucleotides are expressed in hemic, immune, reproductive, and urinary tract tissues. Accordingly, compositions comprising LP218 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and 20 intervention of schizophrenia [Li, *Mol. Psychiatry* 5(1):77-84 (2000)], hypocalcemia [Garabedian, et al., *Genet Couns.* 10(4):389-94 (1999)], rhabdoid tumor [Zhou, et al., *Gene* 241(1):133-41 (2000)], DiGeorge/velo-cardio-facial syndrome [Amati, et al., *Eur. J. Hum. Genet.* 7(8):903-9 (1999)], 25 congenital heart disease [Borgmann, et al., *Eur. J. Pediatr.* 158(12):958-63 (1999)], and abdominal lymphatic dysplasia [Mansir, et al., *Genet. Couns.* 10(1):67-70 (1999)], oesophageal atresia [Digilio, et al., *J. Med. Genet.* 36(2):137-9 (1999)].

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9) LP251(a) and LP251(b)

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In another embodiment, polypeptides comprising the amino acid sequence of the open reading frames encoded by the polynucleotide sequences as shown in SEQ ID NO:19 and SEQ ID NO:33 are contemplated by the present invention.

5 Specifically, LP251(a) and LP251(b) polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:20 and SEQ ID NO:34, respectively, as well as fragments, variants, and derivatives thereof. Accordingly, LP251(a) and LP251(b) polynucleotides comprising 10 polynucleotides as identified in SEQ ID NO:19 or SEQ ID NO:33 are also contemplated by the present invention.

The LP251 polypeptides as shown in SEQ ID NO:20 and SEQ ID NO:34 share sequence similarity with aqualysin I precursor, a subtilisin-type serine protease which is 15 secreted into the culture medium by *Thermus aquaticus* YT-1, an extremely thermophilic gram-negative bacterium [Terada, et al., *J. Biol. Chem.* 265(12):6576-81 (1990)].

The gene encoding the disclosed polypeptides has been localized to chromosome 1p33-p34.3. Accordingly, 20 compositions comprising LP251 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of breast cancer [Emi, et al., *Genes Chromosomes Cancer* 26(2):134-41 (1999)], myelodysplastic syndromes including but not limited to thrombocytopenia and 25 abnormal megakaryopoiesis [Jondeau, et al., *Leukemia* 10(11):1692-5 (1996)], Schnyder's crystalline corneal dystrophy [Shearman, et al., *Hum. Mol. Genet.* 5(10):1667-72 1996], tumorigenesis including, but not limited to, colorectal cancer [Praml, et al., *Oncogene* 11(7):1357-62 30 (1995)], Schwartz-Jampel syndrome [Nicole, *Hum. Mol. Genet.* 4(9):1633-6 (1995)], and autosomal dominant hypercholesterolemia.

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emia [Varret, et al., *Am. J. Hum. Genet.* 64(5):1378-87 (1999)].

Furthermore, LP251 polynucleotides are mainly expressed in skin and liver. Accordingly, compositions comprising 5 LP251 polypeptides, polynucleotides, and/or antibodies are generally useful for the treatment of defects in or wounds to tissues including, but not limited to skin and liver.

10) LP252

10 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:21 are contemplated by the present invention. Specifically, LP252 polypeptides of the present invention comprise the amino 15 acid sequence as shown in SEQ ID NO:22, as well as fragments, variants, and derivatives thereof. Accordingly, LP252 polynucleotides comprising polynucleotides as identified in SEQ ID NO:21 are also contemplated by the present invention.

20 The LP252 polypeptide as shown in SEQ ID NO:22 shares sequence similarity with thyroid hormone-induced protein B precursor. Furthermore, the gene encoding the disclosed polypeptide has been localized to chromosome 9p12-13. Accordingly, compositions comprising LP252 polypeptides, 25 polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of ectrodactyly, ectodermal dysplasia and cleft lip/palate syndrome [Fukushima, et al., *Clin. Genet.* 44(1):50 (1993); Hasegawa, et al., *Clin. Genet.* 40(3):202-6 (1991)]; and cancer, including, but not limited 30 to, kidney cancer and carcinoma of the respiratory tract [Schraml, et al., *J. Pathol.* 190(4):457-61 (2000); Higashi, et al., *Genes Chromosomes Cancer* 3(1):21-3 (1991)].

11) LP223(a) and (b)

In another embodiment, polypeptides comprising the amino acid sequences of the open reading frames encoded by 5 the polynucleotide sequences as shown in SEQ ID NO:25 and SEQ ID NO:37 are contemplated by the present invention. Specifically, LP223(a) and LP223(b) polypeptides of the present invention comprise the amino acid sequences as shown in SEQ ID NO:26 and SEQ ID NO:38, respectively, as well as 10 fragments, variants, and derivatives thereof. Accordingly, LP223(a) and LP223(b) polynucleotides comprising polynucleotides as identified in SEQ ID NO:25 and SEQ ID NO:37 are also contemplated by the present invention. The LP223(a) and LP223(b) polypeptides as shown in SEQ ID NO:26 15 and SEQ ID NO:38 share sequence similarity with a human secreted protein sequence disclosed in WO 2000/04140.

The present invention also provides isolated LP223 polypeptides as described herein, wherein the polypeptides have at least one activity, such as, but not limited to, 20 inducing cellular proliferation, synapse formation, neurotransmission, learning, cognition, homeostasis, neuronal outgrowth, differentiation or survival, or tissue regeneration including but not limited to neural tissue regeneration. An LP223 polynucleotide, polypeptide, and/or 25 antibody can thus be screened for a corresponding activity according to known methods.

The present invention also provides a composition comprising an isolated LP223 nucleic acid, polypeptide, and/or antibody as described herein and a carrier or 30 diluent. The carrier or diluent can optionally be pharmaceutically acceptable, according to known methods. LP223 polynucleotides and polypeptides are expressed in

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nervous tissues and appear to play a role in neurodegenerative diseases, behavioral disorders, and/or inflammatory conditions. Accordingly, compositions comprising LP223 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of diseases, disorders, and/or conditions including, but not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system.

12) LP255(a) and LP255(b)

In another embodiment, polypeptides comprising the amino acid sequences of the open reading frames encoded by the polynucleotide sequences as shown in SEQ ID NO:27 and SEQ ID NO:35 are contemplated by the present invention. Specifically, LP255(a) and LP255(b) polypeptides of the present invention comprise the amino acid sequences as shown in SEQ ID NO:28 and SEQ ID NO:36, respectively, as well as fragments, variants, and derivatives thereof. Accordingly, LP255(a) and LP255(b) polynucleotides comprising polynucleotides as identified in SEQ ID NO:27 and SEQ ID

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NO:35 are also contemplated by the present invention. The LP255(a) and LP255(b) polypeptides as shown in SEQ ID NO:28 and SEQ ID NO:36 share sequence similarity with a human secreted protein sequence disclosed in WO 99/14328 as
5 PRO332.

The present invention also provides isolated LP255 polypeptides as described herein, wherein the polypeptides have at least one activity, such as, but not limited to, promoting cell growth. An LP255 polynucleotide,
10 polypeptide, and/or antibody can thus be screened for a corresponding activity according to known methods.

The present invention also provides a composition comprising an isolated LP255 nucleic acid, polypeptide, and/or antibody as described herein and a carrier or
15 diluent. The carrier or diluent can optionally be pharmaceutically acceptable, according to known methods. LP255 polynucleotides and polypeptides are expressed in nervous tissues and appear to play a role in neurological disorders. Accordingly, compositions comprising LP255
20 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of diseases, disorders, and/or conditions arising from Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases,
25 peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder learning disabilities, ALS, psychoses, autism, and
30 altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

13) LP244

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:29 are 5 contemplated by the present invention. Specifically, LP244 polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:30, as well as fragments, variants, and derivatives thereof. Accordingly, LP244 polynucleotides comprising polynucleotides as 10 identified in SEQ ID NO:29 are also contemplated by the present invention.

The gene encoding the LP244 polypeptide has been localized to chromosome 19 and is predominantly expressed in embryonic structures. The LP244 polypeptide as shown in SEQ 15 ID NO:30 appears to be a novel shortened splice-variant of the human Epstein-Barr virus induced gene 3 (EBI3; GenBank accession no. NP_005746) wherein the first 67 amino acids of the LP244 polypeptide are identical to those of EBI3. EBI3 is reported to be a hematopoietin receptor family 20 member related to the p40 subunit of interleukin-12 and to the ciliary neurotrophic factor receptor, whose expression is induced in B lymphocytes by Epstein-Barr virus (EBV) infection [Devergne, et al., *J. Virology* 70(2):1143-53 (1996)]. The gene encodes a 34-kDa glycoprotein which lacks 25 a membrane-anchoring motif and is secreted. Despite the absence of a membrane-anchoring motif and of cysteines likely to mediate covalent linkage to an integral membrane protein, EBI3 is also present on the plasma membrane of EBV-transformed B lymphocytes and of transfected cells. Most 30 newly synthesized EBI3 is retained in the endoplasmic reticulum in an endoglycosidase H-sensitive form associated with the molecular chaperone calnexin and with a novel 60-

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kDa protein. EBI3 is expressed *in vivo* by scattered cells in interfollicular zones of tonsil tissue, by cells associated with sinusoids in perifollicular areas of spleen tissue, and at very high levels by placental syncytiotrophoblasts. EBI3 expression *in vitro* is induced in EBV-negative cell lines by expression of the EBV latent infection membrane protein-1 and in peripheral blood mononuclear cells by pokeweed mitogen stimulation. EBI3 maps to chromosome 19p13.2/3, near genes encoding the erythropoietin receptor and the cytokine receptor-associated kinase, Tyk2. EBI3 synthesis by trophoblasts and by EBV-transformed cells and similarities to interleukin-12 p40 are compatible with a role for EBI3 in regulating cell-mediated immune responses. LP244 therefore may function as a modulator of EBI3 activity. Administration of a soluble form of LP244 would interfere with the effect of its endogenous ligand on the cells, since the ligand would not bind to the endogenous membrane bound LP244 as freely. Hence, an aspect of the present invention is the treatment of pathological conditions caused by excessive expression of LP244 polypeptides by adding an amount of soluble LP244 polypeptides sufficient to inhibit binding of a cytokine to the aforementioned cells. This methodology can also be modified, and the soluble receptor can also be used as a screening agent for pharmaceuticals. Briefly, a pharmaceutical which works as an LP244 antagonist can do so by blocking the binding of endogenous ligand to the LP244. Prior to determining whether a material would be effective *in vivo*, one may use the purified LP244 polypeptide in connection with a potential pharmaceutical to determine if there is binding. If there is in fact binding, further testing may be indicated.

Expression of recombinant polypeptides in high levels and its use as an antigen allows production of additional neutralizing monoclonal and polyclonal antibodies. Such neutralizing antibodies can be used in *in vivo* model

5 settings to elucidate the role that LP244 and its ligand play in normal as well as pathologic immune responses (i.e., disease states that are aggravated by activated T- and NK-cells like autoimmune diseases, graft versus host disease, and rheumatoid arthritis). Thus, purified LP244 polypeptides, polynucleotides, and/or antibodies compositions will

10 be useful in diagnostic assays for LP244 and its ligand, and also in raising antibodies to LP244 for use in diagnosis or therapy. More specifically, compositions comprising LP244 polypeptides, polynucleotides, and/or antibodies are useful

15 for diagnosis, treatment and intervention of diseases, disorders, and/or conditions including, but not limited to, infectious diseases, hypothyroidism, anemia, sepsis, gram negative bacteremia, allergic responses, allergic autoimmune diseases, type 1 diabetes, Th1-dependent insulitis,

20 inflammation, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, liver failure, ARDS, cancers, leukemia, and immuno-deficiency, arthritis, leukemia, lymphomas, immuno-suppression, immunity, humoral immunity, myelosuppression, periodontal disease, and osteoarthritis.

25 LP244 polypeptides, polynucleotides, and/or antibodies can be administered, for example, for the purpose of suppressing immune responses in a human. A variety of diseases or conditions are caused by an immune response to alloantigen, including allograft rejection and graft-versus-

30 host reaction. In alloantigen-induced immune responses, soluble LP244 polypeptides may suppress lymphoproliferation and inflammation which result upon activation of T cells.

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Soluble LP244 polypeptides may therefore be used to effectively suppress alloantigen-induced immune responses in the clinical treatment of, for example, rejection of allografts (such as skin, kidney, and heart transplants), 5 and graft-versus-host reactions in patients who have received bone marrow transplants.

LP244 polypeptides, polynucleotides, and/or antibodies may also be used in clinical treatment of autoimmune dysfunctions, such as rheumatoid arthritis, diabetes and 10 multiple sclerosis, which are dependent upon the activation of T cells against antigens not recognized as being indigenous to the host. LP244 polypeptides, polynucleotides, and/or antibodies may also be useful in treatment of septic shock in which interferon gamma produced in response to 15 various interleukins plays a central role in causing morbidity and mortality [Doherty, et al., *J. Immunol.* 149:1666 (1992)]. In addition, compositions comprising soluble LP244 compositions may be used directly in therapy to bind or scavenge endogenous LP244 ligands, thereby 20 providing a means for regulating the immune or inflammatory activities. In its use to prevent or reverse pathologic immune responses, soluble LP244 polypeptides can be combined with other cytokine antagonists such as antibodies to the other known interleukin receptors, soluble interleukin 25 receptors, soluble TNF (tumor necrosis factor) receptors, and/or interleukin receptor antagonists, and the like.

14) **LP186**

In another embodiment, polypeptides comprising the 30 amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:31 are contemplated by the present invention. Specifically, LP186

polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:32, as well as fragments, variants, and derivatives thereof. Accordingly, LP186 polynucleotides comprising polynucleotides as 5 identified in SEQ ID NO:31 are also contemplated by the present invention.

The LP186 polypeptide as shown in SEQ ID NO:32 shares sequence similarity with the human delta homologue, DLL3 [Bulman, et al., *Nature Genetics* 24(4):438-41 (2000)]. 10 Mutations in the human delta homologue, DLL3, cause axial skeletal defects in spondylocostal dysostosis. Two of the mutations predict truncations within conserved extracellular domains. The third is a missense mutation in a highly conserved glycine residue of the fifth epidermal growth 15 factor (EGF) repeat, which has revealed an important functional role for this domain. Spondylocostal dysostosis (SD) is a group of vertebral malsegmentation syndromes with reduced stature resulting from axial skeletal defects. SD is characterized by multiple hemivertebrae, rib fusions and 20 deletions with a non-progressive kyphoscoliosis. Dll3 is mutated in the X-ray-induced mouse mutant pudgy (pu), causing a variety of vertebrocostal defects similar to SD phenotypes [Kusumi, et al., *Nature Genetics* 19(3):274-8 (1998)]. These mutations highlight the critical role of the 25 Notch signalling pathway and its components in patterning the mammalian axial.

LP186 polypeptide-encoding polynucleotide sequences are primarily expressed in the nervous system. Thus, polynucleotides, polypeptides, and antibodies corresponding 30 to this gene are useful for diagnosis, treatment and intervention of diseases, disorders, and conditions of the nervous system. Thus, the present sequence represents a

polypeptide which suppresses proliferation and differentiation of undifferentiated cells such as neurons and blood cells. The polypeptide may be used for the prevention and control of disorders involving undifferentiated cells, such 5 as leukaemia and malignant tumours, and improvement of blood formation, e.g., after immunosuppression.

The polynucleotides and polypeptides of the present invention are designated herein as "LP polynucleotides" or 10 "LP polypeptide-encoding polynucleotides" and "LP polypeptides." When immediately followed by a numerical designation (i.e., LP105), the term "LP" refers to a specific group of molecules as defined herein. A complete designation wherein the term "LP" is immediately followed 15 by a numerical designation and a molecule type (i.e., LP105 polypeptide) refers to a specific type of molecule within the designated group of molecules as designated herein.

The terms "LP polypeptide-encoding polynucleotides" or "LP polynucleotides" and "LP polypeptides" wherein the term 20 "LP" is followed by an actual numerical designation as used herein encompass novel polynucleotides and polypeptides, respectively, which are further defined herein. The LP molecules described herein may be isolated from a variety of sources including, but not limited to human tissue 25 types, or prepared by recombinant or synthetic methods.

One aspect of the present invention provides an isolated nucleic acid molecule comprising a polynucleotide which encodes an LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, 30 LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), or LP223(b) polypeptide as defined herein. In a preferred embodiment of the present invention, the isolated

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nucleic acid comprises 1) a polynucleotide encoding an LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), or LP223(b) 5 polypeptide having an amino acid sequence as shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38, respectively; 2) a polynucleotide complementary to such encoding nucleic acid sequences, and which remain stably bound to them under at least moderate, 10 and optionally, high stringency conditions; or 3) any fragment and/or variant of 1) or 2).

The term "LP polypeptide" specifically encompasses truncated or secreted forms of an LP polypeptide, (e.g., soluble forms containing, for instance, an extracellular 15 domain sequence), variant forms (e.g., alternatively spliced forms) and allelic variants of an LP polypeptide.

In one embodiment of the invention, the native sequence LP polypeptide is a full-length or mature LP polypeptide comprising amino acids as shown in SEQ ID NO:2, 20 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38. The predicted signal peptides are indicated in the sequence listing of the present application by negative integers below the amino acids disclosed for a particular polypeptide. Also, while the LP polypeptides 25 disclosed herein are shown to begin with a methionine residue designated as amino acid position 1, it is conceivable and possible that another methionine residue located either upstream or downstream from amino acid position 1 may be employed as the starting amino acid 30 residue.

A "portion" of an LP polypeptide sequence is at least about 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80,

85, 90, 95, or 100 contiguous amino acid residues in length.

"LP polypeptide variant" is intended to refer to an "active" LP polypeptide, wherein activity is as defined 5 herein, having at least about 90% amino acid sequence identity with an LP polypeptide having a deduced amino acid sequences as shown above. Such LP polypeptide variants include, for instance, LP polypeptides, wherein one or more amino acid residues are added, substituted or deleted, at 10 the N- or C-terminus or within the sequences shown.

Ordinarily, an LP polypeptide variant will have at least about 90% amino acid sequence identity, preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least 15 about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least 20 about 98% sequence identity, yet more preferably at least about 99% amino acid sequence identity with the amino acid sequence described, with or without the signal peptide.

"Percent (%) amino acid sequence identity" with respect to the LP amino acid sequences identified herein is 25 defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in an LP polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering 30 any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various

ways that are within the skill in the art, for instance, using publicly available computer software such as ALIGN, ALIGN-2, Megalign (DNASTAR) or BLAST (e.g., Blast, Blast-2, WU-Blast-2) software. Those skilled in the art can 5 determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For example, the percent identity values used herein are generated using WU-BLAST-2 [Altschul, et al., 10 *Methods in Enzymology* 266:460-80 (1996)]. Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1; overlap fraction = 0.125; word threshold 15 (T) = 11; and scoring matrix = BLOSUM 62. For purposes herein, a percent amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acid residues between the amino acid sequence of the LP polypeptide of interest and the comparison amino acid 20 sequence of interest (i.e., the sequence against which the LP polypeptide of interest is being compared) as determined by WU-BLAST-2, by (b) the total number of amino acid residues of the LP polypeptide of interest, respectively.

An "LP variant polynucleotide," "LP polynucleotide 25 variant," or "LP variant nucleic acid sequence" are intended to refer to an nucleic acid molecule as defined below having at least about 75% nucleic acid sequence identity with the polynucleotide sequence as shown in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 30 29, 31, 33, 35, or 37. Ordinarily, an LP polynucleotide variant will have at least about 75% nucleic acid sequence identity, more preferably at least about 80% nucleic acid

sequence identity, yet more preferably at least about 81% nucleic acid sequence identity, yet more preferably at least about 82% nucleic acid sequence identity, yet more preferably at least about 83% nucleic acid sequence

5 identity, yet more preferably at least about 84% nucleic acid sequence identity, yet more preferably at least about 85% nucleic acid sequence identity, yet more preferably at least about 86% nucleic acid sequence identity, yet more preferably at least about 87% nucleic acid sequence

10 identity, yet more preferably at least about 88% nucleic acid sequence identity, yet more preferably at least about 89% nucleic acid sequence identity, yet more preferably at least about 90% nucleic acid sequence identity, yet more preferably at least about 91% nucleic acid sequence

15 identity, yet more preferably at least about 92% nucleic acid sequence identity, yet more preferably at least about 93% nucleic acid sequence identity, yet more preferably at least about 94% nucleic acid sequence identity, yet more preferably at least about 95% nucleic acid sequence

20 identity, yet more preferably at least about 96% nucleic acid sequence identity, yet more preferably at least about 97% nucleic acid sequence identity, yet more preferably at least about 98% nucleic acid sequence identity, yet more preferably at least about 99% nucleic acid sequence

25 identity with the nucleic acid sequences shown above. Variants specifically exclude or do not encompass the native nucleotide sequence, as well as those prior art sequences that share 100% identity with the nucleotide sequences of the invention.

30 "Percent (%) nucleic acid sequence identity" with respect to the LP polynucleotide sequences identified herein is defined as the percentage of nucleotides in a

candidate sequence that are identical with the nucleotides in the LP polynucleotide sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for 5 purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as ALIGN, Align-2, Megalign (DNASTAR), or BLAST (e.g., Blast, Blast-2) 10 software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % nucleic acid identity values are 15 generated using the WU-BLAST-2 (BlastN module) program [Altschul, et al., *Methods in Enzymology* 266:460-80 (1996)]. Most of the WU-BLAST-2 search parameters are set to the default values. Those not set default values, i.e., the adjustable parameters, are set with the following 20 values: overlap span = 1; overlap fraction = 0.125; word threshold (T) = 11; and scoring matrix = BLOSUM62. For purposes herein, a percent nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of 25 the LP polypeptide-encoding nucleic acid molecule of interest and the comparison nucleic acid molecule of interest (i.e., the sequence against which the LP polypeptide-encoding nucleic acid molecule of interest is being compared) as determined by WU-BLAST-2, by (b) the 30 total number of nucleotides of the LP polypeptide-encoding nucleic acid molecule of interest.

In other embodiments, the LP variant polypeptides are encoded by nucleic acid molecules which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding the full-length LP polypeptide as shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38. This scope of variant polynucleotides specifically excludes those sequences that are known as of the filing and/or priority dates of the present application.

The term "mature protein" or "mature polypeptide" as used herein refers to the form(s) of the protein produced by expression in a mammalian cell. It is generally hypothesized that once export of a growing protein chain across the rough endoplasmic reticulum has been initiated, proteins secreted by mammalian cells have a signal peptide (SP) sequence which is cleaved from the complete polypeptide to produce a "mature" form of the protein. Oftentimes, cleavage of a secreted protein is not uniform and may result in more than one species of mature protein.

The cleavage site of a secreted protein is determined by the primary amino acid sequence of the complete protein and generally cannot be predicted with complete accuracy. Methods for predicting whether a protein has an SP sequence, as well as the cleavage point for that sequence, are available. A cleavage point may exist within the N-terminal domain between amino acid 10 and amino acid 35. More specifically the cleavage point is likely to exist after amino acid 15 but before amino acid 30, more likely after amino acid 27. As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Optimally, cleavage sites for a secreted

protein are determined experimentally by amino-terminal sequencing of the one or more species of mature proteins found within a purified preparation of the protein.

The term "positives," in the context of sequence comparison performed as described above, includes residues in the sequences compared that are not identical but have similar properties (e.g., as a result of conservative substitutions). The percent identity value of positives is determined by the fraction of residues scoring a positive value in the BLOSUM 62 matrix. This value is determined by dividing (a) the number of amino acid residues scoring a positive value in the BLOSUM62 matrix of WU-BLAST-2 between the LP polypeptide amino acid sequence of interest and the comparison amino acid sequence (i.e., the amino acid sequence against which the LP polypeptide sequence is being compared) as determined by WU-BLAST-2, by (b) the total number of amino acid residues of the LP polypeptide of interest.

"Isolated," when used to describe the various polypeptides disclosed herein, means a polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Preferably, the isolated polypeptide is free of association with all components with which it is naturally associated. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2)

to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of 5 the LP polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated LP polypeptide-encoding nucleic acid" or "isolated LP nucleic acid" is a nucleic acid molecule that 10 is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the nucleic acid. Such an isolated nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated 15 nucleic acid molecules therefore are distinguished from the nucleic acid molecule as it exists in natural cells. However, an isolated LP polypeptide-encoding nucleic acid molecule includes LP polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express LP 20 polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid 25 sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the 30 transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably

linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation 5 at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

The term "amino acid" is used herein in its broadest sense, and includes naturally occurring amino acids as well 10 as non-naturally occurring amino acids, including amino acid analogs and derivatives. The latter includes molecules containing an amino acid moiety. One skilled in the art will recognize, in view of this broad definition, that reference herein to an amino acid includes, for 15 example, naturally occurring proteogenic L-amino acids; D-amino acids; chemically modified amino acids such as amino acid analogs and derivatives; naturally-occurring non-proteogenic amino acids such as norleucine, beta-alanine, ornithine, etc.; and chemically synthesized compounds 20 having properties known in the art to be characteristic of amino acids. As used herein, the term "proteogenic" indicates that the amino acid can be incorporated into a peptide, polypeptide, or protein in a cell through a metabolic pathway.

25 The incorporation of non-natural amino acids, including synthetic non-native amino acids, substituted amino acids, or one or more D-amino acids into the LP peptides, polypeptides, or proteins of the present invention ("D-LP polypeptides") is advantageous in a number 30 of different ways. D-amino acid-containing peptides, polypeptides, or proteins exhibit increased stability *in vitro* or *in vivo* compared to L-amino acid-containing

counterparts. Thus, the construction of peptides, polypeptides, or proteins incorporating D-amino acids can be particularly useful when greater intracellular stability is desired or required. More specifically, D-peptides, 5 polypeptides, or proteins are resistant to endogenous peptidases and proteases, thereby providing improved bioavailability of the molecule and prolonged lifetimes *in vivo* when such properties are desirable. When it is desirable to allow the peptide, polypeptide, or protein to 10 remain active for only a short period of time, the use of L-amino acids therein will permit endogenous peptidases, proteases, etc., in a cell to digest the molecule *in vivo*, thereby limiting the cell's exposure to the molecule. Additionally, D-peptides, polypeptides, or proteins cannot 15 be processed efficiently for major histocompatibility complex class II-restricted presentation to T helper cells, and are therefore less likely to induce humoral immune responses in the whole organism.

In addition to using D-amino acids, those of ordinary 20 skill in the art are aware that modifications in the amino acid sequence of a peptide, polypeptide, or protein can result in equivalent, or possibly improved, second generation peptides, polypeptides, or proteins, that display equivalent or superior functional characteristics 25 when compared to the original amino acid sequences.

Alterations in the LP peptides, polypeptides, or proteins of the present invention can include one or more amino acid insertions, deletions, substitutions, truncations, fusions, shuffling of subunit sequences, and the like, either from 30 natural mutations or human manipulation, provided that the sequences produced by such modifications have substantially the same (or improved or reduced, as may be desirable)

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activity(ies) as the naturally-occurring counterpart sequences disclosed herein.

One factor that can be considered in making such changes is the hydropathic index of amino acids. The 5 importance of the hydropathic amino acid index in conferring interactive biological function on a protein has been discussed by Kyte and Doolittle [J. Mol. Biol. 157:105-32 (1982)]. It is accepted that the relative hydropathic character of amino acids contributes to the 10 secondary structure of the resultant protein. This, in turn, affects the interaction of the protein with molecules such as enzymes, substrates, receptors, ligands, DNA, antibodies, antigens, etc. Based on its hydrophobicity and charge characteristics, each amino acid has been assigned a 15 hydropathic index as follows: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); 20 glutamate/glutamine/aspartate/asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

As is known in the art, certain amino acids in a peptide, polypeptide, or protein can be substituted for other amino acids having a similar hydropathic index or 25 score and produce a resultant peptide, polypeptide, or protein having similar biological activity, i.e., which still retains biological functionality. In making such changes, it is preferable that amino acids having hydropathic indices within ± 2 are substituted for one 30 another. More preferred substitutions are those wherein the amino acids have hydropathic indices within ± 1 . Most

preferred substitutions are those wherein the amino acids have hydropathic indices within ± 0.5 .

Like amino acids can also be substituted on the basis of hydrophilicity. U.S. Patent 4,554,101 discloses that 5 the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein. The following hydrophilicity values have been assigned to amino acids: arginine/lysine (+3.0); aspartate/glutamate (+3.0 \pm 1); 10 serine (+0.3); asparagine/glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 \pm 1); alanine/histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine/isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); and tryptophan (-3.4). Thus, one amino acid in a 15 peptide, polypeptide, or protein can be substituted by another amino acid having a similar hydrophilicity score and still produce a resultant peptide, polypeptide, or protein having similar biological activity, i.e., still retaining correct biological function. In making such 20 changes, amino acids having hydropathic indices within ± 2 are preferably substituted for one another, those within ± 1 are more preferred, and those within ± 0.5 are most preferred.

As outlined above, amino acid substitutions in the LP 25 polypeptides of the present invention can be based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, etc. Exemplary substitutions that take various of the foregoing characteristics into 30 consideration in order to produce conservative amino acid changes resulting in silent changes within the present

peptides, polypeptides, or proteins can be selected from other members of the class to which the naturally occurring amino acid belongs. Amino acids can be divided into the following four groups: (1) acidic amino acids; (2) basic 5 amino acids; (3) neutral polar amino acids; and (4) neutral non-polar amino acids. Representative amino acids within these various groups include, but are not limited to: (1) acidic (negatively charged) amino acids such as aspartic acid and glutamic acid; (2) basic (positively charged) 10 amino acids such as arginine, histidine, and lysine; (3) neutral polar amino acids such as glycine, serine, threonine, cysteine, cystine, tyrosine, asparagine, and glutamine; and (4) neutral non-polar amino acids such as alanine, leucine, isoleucine, valine, proline, phenyl- 15 alanine, tryptophan, and methionine.

It should be noted that changes which are not expected to be advantageous can also be useful if these result in the production of functional sequences. Since small peptides 20 polypeptides, and some proteins can be easily produced by conventional solid phase synthetic techniques, the present invention includes peptides, polypeptides, or proteins such as those discussed herein, containing the amino acid modifications discussed above, alone or in various combinations. To the extent that such modifications can be 25 made while substantially retaining the activity of the peptide, polypeptide, or protein, they are included within the scope of the present invention. The utility of such modified peptides, polypeptides, or proteins can be determined without undue experimentation by, for example, 30 the methods described herein.

While biologically functional equivalents of the present LP polypeptides can have any number of conservative

or non-conservative amino acid changes that do not significantly affect their activity(ies), or that increase or decrease activity as desired, 40, 30, 20, 10, 5, or 3 changes, such as 1 to 30 changes or any range or value 5 therein, may be preferred. In particular, ten or fewer amino acid changes may be preferred. More preferably, seven or fewer amino acid changes may be preferred; most preferably, five or fewer amino acid changes may be preferred. The encoding nucleotide sequences (gene, plasmid 10 DNA, cDNA, synthetic DNA, or mRNA, for example) will thus have corresponding base substitutions, permitting them to code on expression for the biologically functional equivalent forms of the LP polypeptides. In any case, the LP peptides, polypeptides, or proteins exhibit the same or 15 similar biological or immunological activity(ies) as that(those) of the LP polypeptides specifically disclosed herein, or increased or reduced activity, if desired. The activity(ies) of the variant LP polypeptides can be determined by the methods described herein. Variant LP 20 polypeptides biologically functionally equivalent to those specifically disclosed herein have activity(ies) differing from those of the presently disclosed molecules by about $\pm 50\%$ or less, preferably by about $\pm 40\%$ or less, more preferably by about $\pm 30\%$ or less, more preferably by about 25 $\pm 20\%$ or less, and even more preferably by about $\pm 10\%$ or less, when assayed by the methods disclosed herein.

Amino acids in an LP polypeptide of the present invention that are essential for activity can be identified by methods known in the art, such as site-directed 30 mutagenesis or alanine-scanning mutagenesis [Cunningham and Wells, *Science* 244:1081-5 (1989)]. The latter procedure introduces single alanine mutations at every residue in the

molecule. The resulting mutant molecules are then tested for biological activity. Sites that are critical for ligand-protein binding can also be identified by structural analysis such as crystallization, nuclear magnetic resonance, or photoaffinity labeling [Smith, et al., *J. Mol. Biol.* 224:899-904 (1992); de Vos, et al., *Science* 255:306-12 (1992)].

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer nucleic acid probes required higher temperatures for proper annealing, while shorter nucleic acid probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature that can be used. As a result, it follows that higher relative temperatures would tend to make the reactions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel, et al., *Current Protocols in Molecular Biology*, Wiley Interscience Publishers (1995).

"Stringent conditions" or "high stringency conditions," as defined herein, may be identified by those that (1) employ low ionic strength and high temperature for washing, for example, 15 mM sodium chloride/1.5 mM sodium citrate/0.1% sodium dodecyl sulfate at 50 degrees C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1%

bovine serum albumin/0.1% ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride/75 mM sodium citrate at 42 degrees C; or (3) employ 50% formamide, 5X SSC (750 mM sodium chloride, 5 75 mM sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5X Denhardt's solution, sonicated salmon sperm DNA (50 µg/mL), 0.1% SDS, and 10% dextran sulfate at 42 degrees C with washes at 42 degrees C in 0.2X SSC (30 mM sodium chloride/3 mM sodium citrate) and 10 50% formamide at 55 degrees C, followed by a high-stringency wash consisting of 0.1X SSC containing EDTA at 55 degrees C.

"Moderately stringent conditions" may be identified as described by Sambrook, et al. [Molecular Cloning: A 15 Laboratory Manual, New York: Cold Spring Harbor Press, (1989)], and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight 20 incubation at 37 degrees C in a solution comprising: 20% formamide, 5X SSC (750 mM sodium chloride, 75 mM sodium citrate), 50 mM sodium phosphate at pH 7.6, 5X Denhardt's solution, 10% dextran sulfate, and 20 mg/mL denatured sheared salmon sperm DNA, followed by washing the filters 25 in 1X SSC at about 37 to 50 degrees C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc., as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" where used herein refers to 30 a chimeric polypeptide comprising an LP polypeptide, or domain sequence thereof, fused to a "tag polypeptide." The tag polypeptide has enough residues to provide an epitope

against which an antibody may be made, or which can be identified by some other agent, yet is short enough such that it does not interfere with the activity of the LP polypeptide. The tag polypeptide preferably is also fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about eight to about fifty amino acid residues (preferably, between about ten to about twenty residues).

10 As used herein, the term "immunoadhesin," sometimes referred to as an Fc fusion, designates antibody-like molecules that combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains.

15 Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part

20 of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3 or IgG-4

25 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

"Active" or "activity" for the purposes herein refers to form(s) of LP polypeptide which retain all or a portion of the biologic and/or immunologic activities of native or naturally-occurring LP polypeptide. Elaborating further,

30 "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring LP polypeptide other than the ability

to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring LP polypeptide. An "immunological" activity refers only to the ability to induce the production of an 5 antibody against an antigenic epitope possessed by a native or naturally-occurring LP polypeptide.

The term "antagonist" is used in the broadest sense and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native 10 LP polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native LP polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or 15 antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native LP polypeptides, peptides, ribozymes, anti-sense nucleic acids, small organic molecules, etc. Methods for identifying agonists or antagonists of an LP polypeptide may comprise contacting 20 an LP polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the LP polypeptide.

"Antibodies" (Abs) and "immunoglobulins" (Igs) are 25 glycoproteins having the same structural characteristics. While antibodies exhibit binding specificity to a specific antigen, immunoglobulins include both antibodies and other antibody-like molecules that lack antigen specificity. Polypeptides of the latter kind are, for example, produced 30 at low levels by the lymph system and at increased levels by myelomas. The term "antibody" is used in the broadest sense and specifically covers, without limitation, intact

monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies) formed from at least two intact antibodies, and antibody fragments so long as they exhibit the desired biological activity.

5 The terms "treating," "treatment," and "therapy" as used herein refer to curative therapy, prophylactic therapy, and preventive therapy. An example of "preventive therapy" is the prevention or lessened targeted pathological condition or disorder. Those in need of
10 treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

15 "Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption but, rather, is cyclic in nature.

20 Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

25 A "therapeutically-effective amount" is the minimal amount of active agent (e.g., an LP polypeptide, antagonist or agonist thereof) which is necessary to impart therapeutic benefit to a mammal. For example, a "therapeutically-effective amount" to a mammal suffering or prone to suffering or to prevent it from suffering is such an amount which induces, ameliorates, or otherwise causes an improvement in the pathological symptoms, disease
30 progression, physiological conditions associated with or resistance to succumbing to the aforedescribed disorder.

"Carriers" as used herein include pharmaceutically-acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the 5 physiologically-acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecule weight (less than about 10 residues) 10 polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinyl-pyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, 15 mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN®, polyethylene glycol (PEG), and PLURONIC®.

"Antibody fragments" comprise a portion of an intact 20 antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂ and Fv fragments; diabodies; linear antibodies [Zapata, et al., *Protein Engin.* 8 (10):1057-62 (1995)]; single-chain antibody molecules; and 25 multispecific antibodies formed from antibody fragments.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is 30 in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_HV_L dimer. Collectively, the six CDRs

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confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDR specific for an antigen) has the ability to recognize and bind antigen, although at a lower 5 affinity than the entire binding site.

"Single-chain Fv" or "sFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between 10 the V_H and V_L domain, which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun, *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore, eds., Springer-Verlag, New York, pp. 269-315 (1994).

15 The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow 20 pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404 097; WO 93/11161; and Hollinger, et al., *Proc. Natl. Acad. Sci. USA* 90:6444-8 (1993).

25 An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere 30 with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the

antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or 5 internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue, or preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least 10 one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An "LP polypeptide antibody" or "LP antibody" refers to an antibody as defined herein that recognizes and binds 15 at least one epitope of an LP polypeptide of the present invention. The term "LP polypeptide antibody" or "LP antibody" wherein the term "LP" is followed by a numerical designation refers to an antibody that recognizes and binds to at least one epitope of that particular LP polypeptide 20 as disclosed herein.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as an LP polypeptide or antibody thereto) to a mammal. The components of the 25 liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A "small molecule" is defined herein to have a molecular weight below about 500 daltons.

The term "modulate" means to affect (e.g., either 30 upregulate, downregulate or otherwise control) the level of a signaling pathway. Cellular processes under the control of signal transduction include, but are not limited to,

transcription of specific genes, normal cellular functions, such as metabolism, proliferation, differentiation, adhesion, apoptosis and survival, as well as abnormal processes, such as transformation, blocking of
5 differentiation and metastasis.

An LP polynucleotide can be composed of any polyribonucleotide or polydeoxyribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, the LP polynucleotides can be composed of single- and
10 double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a
15 mixture of single- and double-stranded regions. In addition, LP polynucleotides can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. LP polynucleotides may also contain one or more modified bases or DNA or RNA backbones modified for stability or for
20 other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

25 LP polypeptides can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the gene-encoded amino acids. The LP polypeptides may be modified by either natural processes, such as post-
30 translational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more

detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in the LP polypeptides, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be

5 appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given LP polypeptide. Also, a given LP polypeptide may contain many types of modifications. LP polypeptides may be branched, for example, as a result of ubiquitination, and

10 they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic LP polypeptides may result from post-translation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment

15 of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation,

20 formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing,

25 phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. See, for instance, Creighton, *Proteins - Structure and Molecular Properties*, 2nd Ed., W. H. Freeman and Company, New York

30 (1993); Johnson, *Post-translational Covalent Modification of Proteins*, Academic Press, New York, pp. 1-12 (1983);

Seifter, et al., *Meth. Enzymol.* 182:626-46 (1990); Rattan, et al., *Ann. NY Acad. Sci.* 663:48-62 (1992).

Variations in the full-length sequence LP polypeptide or in various domains of the LP polypeptide described herein can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding LP polypeptide that results in a change in the amino acid sequence of the LP polypeptide as compared with the native sequence LP polypeptide or an LP polypeptide as disclosed herein. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the LP polypeptide. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the LP polypeptide with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of one to five amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity (such as in any of the *in vitro* assays described herein) for activity exhibited by the full-length or mature polypeptide sequence.

LP polypeptide fragments are also provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length or native protein.

5 Certain fragments contemplated by the present invention may lack amino acid residues that are not essential for a desired biological activity of the LP polypeptide.

LP polypeptide fragments may be prepared by any of a number of conventional techniques. Desired peptide

10 fragments may be chemically synthesized. An alternative approach involves generating LP fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable 15 restriction enzymes and isolating the desired fragment.

Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment

20 are employed at the 5' and 3' primers in the PCR.

Preferably, LP polypeptide fragments share at least one biological and/or immunological activity with at least one of the LP polypeptides as shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 25 38.

Covalent modifications of LP polypeptides are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of an LP polypeptide with an organic derivatizing agent 30 that is capable of reacting with selected side chains or the N- or C-terminal residues of an LP polypeptide.

Derivatization with bifunctional agents is useful, for

instance, for crosslinking LP polypeptide to a water-insoluble support matrix or surface for use in the method for purifying anti-LP polypeptide antibodies, and vice-versa. Commonly used crosslinking agents include, e.g.,

5 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as

10 bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithiolpropioimidate].

Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline

15 and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains [Creighton, *Proteins: Structure and Molecular Properties*, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the

20 N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the LP polypeptides included within the scope of this invention comprises altering the native glycosylation pattern of the

25 polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence LP polypeptide and/or adding one or more glycosylation sites that are not present in the native sequences of LP

30 polypeptides. Additionally, the phrase includes qualitative changes in the glycosylation of the native

proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to LP polypeptides may be accomplished by altering the amino acid sequence 5 thereof. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequences of LP polypeptides (for O-linked glycosylation sites). The LP amino acid sequences may optionally be altered through 10 changes at the DNA level, particularly by mutating the DNA encoding the LP polypeptides at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate 15 moieties on the LP polypeptides is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330, and in Aplin and Wriston, *CRC Crit. Rev. Biochem.*, pp. 259-306 (1981).

20 Removal of carbohydrate moieties present on the LP polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art 25 and described, for instance, by Sojar, et al., *Arch. Biochem. Biophys.* 259:52-7 (1987), and by Edge, et al., *Anal. Biochem.* 118:131-7 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as 30 described by Thotakura, et al., *Meth. Enzymol.* 138:350-9 (1987).

Another type of covalent modification of LP comprises linking any one of the LP polypeptides to one of a variety of non-proteinaceous polymers (e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes) in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192, or 4,179,337.

LP polypeptides of the present invention may also be modified in a way to form chimeric molecules comprising an LP polypeptide fused to another heterologous polypeptide or amino acid sequence. In one embodiment, such a chimeric molecule comprises a fusion of an LP polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), or LP223(b) polypeptide. The presence of such epitope-tagged forms of an LP polypeptide can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables an LP polypeptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag.

In an alternative embodiment, the chimeric molecule may comprise a fusion of an LP polypeptide with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule, such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble transmembrane domain deleted or inactivated form of an LP polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment,

the immunoglobulin fusion includes the hinge, CH2 and CH3 or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions, see also U.S. Patent 5,428,130.

5 In yet a further embodiment, the LP polypeptides of the present invention may also be modified in a way to form a chimeric molecule comprising an LP polypeptide fused to a leucine zipper. Various leucine zipper polypeptides have been described in the art. See, e.g., Landschulz, et al.,
10 *Science* 240(4860):1759-64 (1988); WO 94/10308; Hoppe, et al., *FEBS Letters* 344(2-3):191-5 (1994); Abel, et al., *Nature* 341(6237):24-5 (1989). It is believed that use of a leucine zipper fused to an LP polypeptide may be desirable to assist in dimerizing or trimerizing soluble LP
15 polypeptide in solution. Those skilled in the art will appreciate that the zipper may be fused at either the N- or C-terminal end of an LP polypeptide.

20 The description below relates primarily to production of LP polypeptides by culturing cells transformed or transfected with a vector containing an LP polypeptide-encoding nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare LP polypeptides. For instance, the LP polypeptide sequence, or portions thereof, may be
25 produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart, et al., *Solid-Phase Peptide Synthesis*, W.H. Freeman & Co., San Francisco, CA (1969); Merrifield, *J. Am. Chem. Soc.* 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual
30 techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's

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instructions. Various portions of an LP polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to produce a full-length LP polypeptide.

5 DNA encoding an LP polypeptide may be obtained from a cDNA library prepared from tissue believed to possess the LP polypeptide-encoding mRNA and to express it at a detectable level. Libraries can be screened with probes (such as antibodies to an LP polypeptide or

10 oligonucleotides of at least about 20 to 80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook, et al., *Molecular Cloning: A*

15 *Laboratory Manual*, Cold Spring Harbor Laboratory Press, NY (1989). An alternative means to isolate the gene encoding an LP polypeptide is to use PCR methodology [Sambrook, et al., *supra*; Dieffenbach, et al., *PCR Primer: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, NY (1995)].

20 Nucleic acids having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time and, if necessary, using conventional primer extension procedures as described in Sambrook, et al.,

25 *supra*, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

Host cells are transfected or transformed with expression or cloning vectors described herein for LP polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions,

such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of 5 cell cultures can be found in *Mammalian Cell Biotechnology: A Practical Approach*, Butler, ed. (IRL Press, 1991) and Sambrook, et al., supra. Methods of transfection are known to the ordinarily skilled artisan, for example, calcium phosphate and electroporation. General aspects of 10 mammalian cell host system transformations have been described in U.S. Patent 4,399,216. Transformations into yeast are typically carried out according to the method of van Solingen, et al., *J Bact.* 130(2):946-7 (1977) and Hsiao, et al., *Proc. Natl. Acad. Sci. USA* 76(8):3829-33 15 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene or polyornithine, may also be used. For various techniques for transforming mammalian 20 cells, see Keown, et al., *Methods in Enzymology* 185:527-37 (1990) and Mansour, et al., *Nature* 336(6197):348-52 (1988).

Suitable host cells for cloning or expressing the nucleic acid (e.g., DNA) in the vectors herein include 25 prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* strain X1776 (ATCC 31,537); *E. coli* 30 strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*,

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Enterobacter, Erwinia, Klebsiella, Proteus, Salmonella, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710, published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3 110 may be modified to effect a genetic mutation in a gene encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype tonAD; *E. coli* W3110 strain 9E4, which has the complete genotype tonAD ptr3; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype tonAD ptr3 phoADE15 D(argF-lac)169 ompTD degP41kan^R; *E. coli* W3110 strain 37D6, which has the complete genotype tonAD ptr3 phoADE15 D(argF-lac)169 ompTD degP41kan^R rbs7D ilvG; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant degP deletion mutation; and an *E. coli* strain having mutant periplasmic protease as disclosed in U.S. Patent 4,946,783 issued 7 August 1990. Alternatively, *in vivo* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for LP vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* [Beach and Nurse,

Nature 290:140-3 (1981); EP 139,383 published 2 May 1995]; Muyveromyces hosts [U.S. Patent 4,943,529 Fleer, et al., *Bio/Technology* 9(10):968-75 (1991)] such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574) [de Louvencourt, et al., *J. Bacteriol.* 154(2):737-42 (1983)]; *K. fiagilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickeramii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilicola* (ATCC 36,906) [Van den Berg, et al., *Bio/Technology* 8(2):135-9 (1990)]; *K. thermotolerans*, and *K. marxianus*; *yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070) [Sreekrishna, et al., *J. Basic Microbiol.* 28(4):265-78 (1988)]; *Candida*; *Trichoderma reesii* (EP 244,234); *Neurospora crassa* [Case, et al., *Proc. Natl. Acad. Sci. USA* 76(10):5259-63 (1979)]; *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* [Ballance, et al., *Biochem. Biophys. Res. Comm.* 112(1):284-9 (1983); Tilburn, et al., *Gene* 26(2-3):205-21 (1983); Yelton, et al., *Proc. Natl. Acad. Sci. USA* 81(5):1470-4 (1984)] and *A. niger* [Kelly and Hynes, *EMBO J.* 4(2):475-9 (1985)]. Methylotrophic yeasts are selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeast may be found in Antony, *The Biochemistry of Methylotrophs* 269 (1982).

Suitable host cells for the expression of glycosylated LP polypeptides are derived from multicellular organisms.

Examples of invertebrate cells include insect cells such as *Drosophila S2* and *Spodoptera Sp*, *Spodoptera high5* as well as plant cells. Examples of useful mammalian host cell

lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line [293 or 293 cells subcloned for growth in 5 suspension culture, Graham, et al., *J. Gen Virol.*, 36(1):59-74 (1977)]; Chinese hamster ovary cells/-DHFR [CHO, Urlaub and Chasin, *Proc. Natl. Acad. Sci. USA*, 77(7):4216-20 (1980)]; mouse sertoli cells [TM4, Mather, *Biol. Reprod.* 23(1):243-52 (1980)]; human lung cells (W138, 10 ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

LP polypeptides may be produced recombinantly not only 15 directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the 20 vector, or it may be a part of the LP polypeptide-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast 25 secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* cc-factor leaders, the latter described in U.S. Patent 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader 30 (EP 362,179), or the signal described in WO 90/13646. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal

sequences from secreted polypeptides of the same or related species as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for Bacilli.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the LP polypeptide-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described Urlaub and Chasin, *Proc. Natl. Acad. Sci. USA*, 77(7):4216-20 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb, et al., *Nature* 282(5734):39-43 (1979); Kingsman, et al., *Gene* 7(2):141-52 (1979); Tschumper, et al., *Gene* 10(2):157-66 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of

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yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEPC1 [Jones, *Genetics* 85:23-33 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the LP polypeptide-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the P-lactamase and lactose promoter systems [Chang, et al., *Nature* 275(5681):617-24 (1978); Goeddel, et al., *Nature* 281(5732):544-8 (1979)], alkaline phosphatase, a tryptophan (up) promoter system [Goeddel, *Nucleic Acids Res.* 8(18):4057-74 (1980); EP 36,776 published 30 September 1981], and hybrid promoters such as the tat promoter [deBoer, et al., *Proc. Natl. Acad. Sci. USA* 80(1):21-5 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding LP polypeptide.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman, et al., *J. Biol. Chem.* 255(24):12073-80 (1980)] or other glycolytic enzymes [Hess, et al., *J. Adv. Enzyme Reg.* 7:149 (1968); Holland, *Biochemistry* 17(23):4900-7 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol

dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose 5 utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657. LP transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus, 10 adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock 15 promoters, provided such promoters are compatible with the host cell systems.

Transcription of a polynucleotide encoding an LP polypeptide by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers 20 are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, alpha-ketoprotein, and insulin). Typically, however, one will 25 use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The 30 enhancer may be spliced into the vector at a position 5' or 3' to the LP polypeptide coding sequence but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription 5 and for stabilizing the mRNA. Such sequences are commonly available from the 5' and occasionally 3' untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the 10 mRNA encoding LP.

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, *Proc. Natl. Acad. Sci. USA* 77(9):5201-5 15 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA 20 hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

25 Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical 30 staining and/or assay of sample fluids may be either monoclonal or polyclonal and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a

native sequence provided herein or against exogenous sequence fused to an LP polypeptide-encoding DNA and encoding a specific antibody epitope.

Various forms of an LP polypeptide may be recovered from 5 culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g., Triton X-100TM) or by enzymatic cleavage. Cells employed in expression of an LP polypeptide can be disrupted by various physical or chemical means, such 10 as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desireable to purify LP polypeptides from recombinant cell proteins or polypeptides. The following 15 procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reversed-phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex[®] G-75; protein A 20 Sepharose[®] columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of an LP polypeptide. Various methods of protein purification may be employed and such methods are known in the art and described, for example, in Deutscher, *Methods in Enzymology* 25 182:83-9 (1990) and Scopes, *Protein Purification: Principles and Practice*, Springer-Verlag, NY (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular LP polypeptide produced.

30 Nucleotide sequences (or their complement) encoding LP polypeptides have various applications in the art of molecular biology, including uses as hybridization probes,

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in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. LP polypeptide-encoding nucleic acids will also be useful for the preparation of LP polypeptides by the recombinant techniques described 5 herein.

The full-length LP polypeptide-encoding nucleotide sequence (e.g., SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37), or portions thereof, may be useful as hybridization probes for probing 10 a cDNA or genomic library to isolate the full-length LP polypeptide-encoding cDNA or genomic sequences including promoters, enhancer elements and introns of native sequence LP polypeptide-encoding DNA or to isolate still other genes (for instance, those encoding naturally-occurring variants 15 of LP polypeptides or the same from other species) which have a desired sequence identity to the LP polypeptide-encoding nucleotide sequence disclosed in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37. Hybridization techniques are well known in the 20 art and some of which are described in further detail in the Examples below.

Other useful fragments of the LP polypeptide-encoding nucleic acids include anti-sense or sense oligonucleotides comprising a single-stranded nucleic acid sequence (either 25 RNA or DNA) capable of binding to target LP polypeptide-encoding mRNA (sense) of LP polypeptide-encoding DNA (anti-sense) sequences. Anti-sense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of LP polypeptide-encoding DNA. Such a 30 fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an anti-sense or a sense oligonucleotide, based upon

a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen, *Cancer Res.* 48(10):2659-68 (1988) and van der Krol, et al., *Bio/Techniques* 6(10):958-76 (1988).

5 Binding of anti-sense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of
10 transcription or translation, or by other means. The anti-sense oligonucleotides thus may be used to block expression of LP mRNA and therefore any LP polypeptide encoded thereby. Anti-sense or sense oligonucleotides further comprise oligonucleotides having modified sugar-
15 phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of resisting enzymatic degradation)
20 but retain sequence specificity to be able to bind to target nucleotide sequences.

Other examples of sense or anti-sense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in
25 WO 90/10448, and other moieties that increase affinity of the oligonucleotide for a target nucleic acid sequence, such poly-L-lysine. Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or anti-sense
30 oligonucleotides to modify binding specificities of the anti-sense or sense oligonucleotide for the target nucleotide sequence.

Anti-sense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, calcium phosphate-mediated DNA transfection, electroporation, or by 5 using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an anti-sense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either *in vivo* or 10 *ex vivo*. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MSV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated CDTSA, CTSB and DCTSC (see WO 90/13641).

Alternatively, a sense or an anti-sense oligonucleotide 15 may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or anti-sense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

When the amino acid sequence for an LP polypeptide 20 encodes a protein which binds to another protein (for example, where the LP polypeptide functions as a receptor), the LP polypeptide can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or 25 agonists of the binding interaction. Also, the receptor LP polypeptide can be used to isolate correlative ligand(s). Screening assays can be designed to find lead compounds 30 that mimic the biological activity of the LP polypeptides

disclosed herein or a receptor for such LP polypeptides. Typical screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule 5 drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well 10 characterized in the art.

Nucleic acids which encode an LP polypeptide of the present invention or any of its modified forms can also be used to generate either transgenic animals or "knockout" animals which, in turn, are useful in the development and 15 screening of therapeutically useful reagents. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Patents 4,736,866 and 4,870,009. Typically, particular cells would be targeted 20 for an LP transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding an LP polypeptide. 25 Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal 30 is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

Alternatively, non-human homologs of LP polynucleotides can be used to construct a "knockout" animal which has a defective or altered gene encoding a particular LP polypeptide as a result of homologous recombination between the endogenous gene encoding the LP polypeptide and the altered genomic DNA introduced into an embryonic cell of the animal. For example, cDNA encoding an LP polypeptide can be used to clone genomic DNA encoding that LP polypeptide in accordance with established techniques. A portion of the genomic DNA encoding an LP polypeptide can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see, e.g., Thomas and Capecchi, *Cell* 51(3):503-12 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation), and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see, e.g., Li, et al., *Cell* 69(6):915-26 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see, e.g., Bradley, *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed., pp. 113-152 (IRL, Oxford, 1987)]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knockout" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals

can be characterized, for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the native LP polypeptide.

5 Transgenic non-human mammals are useful as an animal models in both basic research and drug development endeavors. Transgenic animals expressing at least one LP polypeptide or nucleic acid can be used to test compounds or other treatment modalities which may prevent, suppress, or 10 cure a pathology or disease associated with at least one of the above mentioned activities. Such transgenic animals can also serve as a model for the testing of diagnostic methods for those same diseases. Furthermore, tissues derived from such transgenic non-human mammals are useful as a source of 15 cells for cell culture in efforts to develop *in vitro* bioassays to identify compounds that modulate LP polypeptide activity or LP polypeptide dependent signaling. Accordingly, another aspect of the present invention contemplates a method of identifying compounds efficacious 20 in the treatment of at least one previously described disease or pathology associated with an LP polypeptide associated activity. A non-limiting example of such a method comprises:

- a) generating a transgenic non-human animal which 25 expresses an LP polypeptide of the present invention and which is, as compared to a wild-type animal, pathologically distinct in some detectable or measurable manner from wild-type version of said non-human mammal;
- b) exposing said transgenic animal to a compound, and;
- c) determining the progression of the pathology in the 30 treated transgenic animal, wherein an arrest, delay, or reversal in disease progression in transgenic animal treated

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with said compound as compared to the progression of the pathology in an untreated control animals is indicative that the compound is useful for the treatment of said pathology.

Another embodiment of the present invention provides a 5 method of identifying compounds capable of inhibiting LP polypeptide activity *in vivo* and/or *in vitro* wherein said method comprises:

- a) administering an experimental compound to an LP polypeptide expressing transgenic non-human animal, or 10 tissues derived therefrom, exhibiting one or more physiological or pathological conditions attributable to the expression of an LP transgene; and
- b) observing or assaying said animal and/or animal tissues to detect changes in said physiological or 15 pathological condition or conditions.

Another embodiment of the invention provides a method for identifying compounds capable of overcoming deficiencies in LP polypeptide activity *in vivo* or *in vitro* wherein said method comprises:

- a) administering an experimental compound to an LP polypeptide expressing transgenic non-human animal, or tissues derived therefrom, exhibiting one or more physiological or pathological conditions attributable to the disruption of the endogenous LP polypeptide-encoding gene; 20
- and
- b) observing or assaying said animal and/or animal tissues to detect changes in said physiological or pathological condition or conditions.

Various means for determining a compound's ability to 30 modulate the activity of an LP polypeptide in the body of the transgenic animal are consistent with the invention. Observing the reversal of a pathological condition in the LP

polypeptide expressing transgenic animal after administering a compound is one such means. Another more preferred means is to assay for markers of LP activity in the blood of a transgenic animal before and after administering an 5 experimental compound to the animal. The level of skill of an artisan in the relevant arts readily provides the practitioner with numerous methods for assaying physiological changes related to therapeutic modulation of LP activity.

10 "Gene therapy" includes both conventional gene therapy, where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA.

15 Anti-sense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has already been shown that short anti-sense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations 20 caused by their restricted uptake by the cell membrane [Zamecnik, et al., *Proc. Natl. Acad. Sci. USA* 83(12):4143-6 (1986)]. The oligonucleotides can be modified to enhance their uptake, e.g., by substituting their negatively charged phosphodiester groups with uncharged groups.

25 There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cell *in vitro* or *in vivo* in the cells of the intended host. Techniques suitable for the 30 transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, micro-injection, cell fusion, DEAE-dextran, the calcium phosphate

precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically, retroviral) vectors and viral coat protein-liposome mediated transfection [Dzau, et al., *Trends in Biotechnology* 11(5):205-10 (1993)]. In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cells, etc.

10 Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g., capsid proteins or fragments thereof trophic for a particular cell type, antibodies for proteins which undergo

15 internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu, et al., *J. Biol. Chem.* 262(10):4429-32 (1987); and Wagner, et al., *Proc. Natl. Acad. Sci. USA* 87(9):3410-4 (1990). For a review of gene marking and gene therapy protocols, see Anderson, *Science* 256(5058):808-13 (1992).

The nucleic acid molecules encoding LP polypeptides or fragments thereof described herein are useful for

25 chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data, are presently available. Each LP polypeptide-encoding nucleic acid molecule of the present invention can be used as a chromosome marker. An LP polypeptide-encoding nucleic acid or fragments thereof can

also be used for chromosomal localization of the gene encoding that LP polypeptide.

The present invention further provides anti-LP polypeptide antibodies. Exemplary antibodies include 5 polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

The anti-LP polypeptide antibodies of the present invention may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled 10 artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal 15 injections. The immunizing agent may include the LP polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include, but are not limited to, 20 keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization 25 protocol may be selected by one skilled in the art without undue experimentation.

The anti-LP polypeptide antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described 30 by Kohler and Milstein, *Nature* 256(5517):495-7 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal is typically immunized with an immunizing agent

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to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

5 The immunizing agent will typically include an LP polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used, if cells of human origin are desired, or spleen cells or lymph node cells are used, if non-human mammalian sources are desired.

10 The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, *Monoclonal Antibodies: Principles and Practice*, Academic Press, pp. 59-103 (1986)]. Immortalized cell lines are usually

15 transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or

20 survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"),

25 which prevents the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred

30 immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, CA, and the American Type

Culture Collection (ATCC), Rockville, MD. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, *J. Immunol.* 133(6):3001-5 (1984); Brodeur, et al., 5 *Monoclonal Antibody Production Techniques and Applications*, Marcel Dekker, Inc., NY, pp. 51-63 (1987)].

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against an LP polypeptide. Preferably, 10 the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding 15 affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Rodbard, *Anal. Biochem.* 107(1):220-39 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and 20 grown by standard methods [Goding, *Monoclonal Antibodies: Principles and Practice*, Academic Press, pp. 59-103 (1986)]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be 25 grown *in vivo* as ascites in a mammal.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced 30 using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains

of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian 5 COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human 10 heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent 4,816,567; Morrison, et al., *Proc. Natl. Acad. Sci. USA* 81(21):6851-5 (1984)] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a 15 non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent 20 antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy 25 chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

30 *In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce

fragments thereof, particularly Fab fragments, can be accomplished using routine techniques known in the art.

The anti-LP polypeptide antibodies of the invention may further comprise humanized antibodies or human

5 antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human

10 immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary-determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the

15 desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported

20 CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin, and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human

25 immunoglobulin [Jones, et al., *Nature* 321(6069):522-5 (1986); Riechmann, et al., *Nature* 332(6162):323-7 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-6 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones, et al., *Nature* 321(6069):522-5 (1986); Riechmann, et al., *Nature* 332(6162):323-7 (1988); Verhoeyen, et al., *Science* 239(4847):1534-6 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent 4,816,567) wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, *J. Mol. Biol.* 227(2):381-8 (1992); Marks, et al., *J. Mol. Biol.* 222(3):581-97 (1991)]. The techniques of Cole, et al., and Boerner, et al., are also available for the preparation of human monoclonal antibodies (Cole, et al., *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985), and Boerner, et al., *J. Immunol.* 147(1):86-95 (1991)).

Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been

partially or complete inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly and antibody repertoire. This 5 approach is described, for example, in U.S. Patents 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks, et al., *Biotechnology* 10(7):779-83 (1992); Lonberg, et al., *Nature* 368(6474):856-9 (1994); Morrison, *Nature* 10 368(6474):812-3 (1994); Fishwild, et al., *Nature Biotechnology* 14(7):845-51 (1996); Neuberger, *Nature Biotechnology* 14(7):826 (1996); Lonberg and Huszar, *Int. Rev. Immunol.* 13(1):65-93 (1995).

Bispecific antibodies are monoclonal, preferably human 15 or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for an LP polypeptide, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit. 20 Methods for making bispecific antibodies are known in the art. Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared [Tutt, et al., *J Immunol.* 147(1):60-9 (1991)].

Heteroconjugate antibodies are also within the scope 25 of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent 4,676,980], and for treatment of HIV infection 30 [WO 91/00360; WO 92/20373]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving

crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-5 mercaptobutyrimidate and those disclosed, for example, in U.S. Patent 4,676,980.

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g., an enzymatically 10 active toxin of bacterial, fungal, plant or animal origin, or fragments thereof, or a small molecule toxin), or a radioactive isotope (i.e., a radioconjugate).

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein coupling 15 agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds, 20 bis-diazonium derivatives (such as bis-2-diazoniumbenzoyl)-ethylenediamine diisocyanates (such as tolylene-2,6-diisocyanate), and bioactive fluorine compounds. For example, a ricin immunotoxin can be prepared as described in Vitetta, et al., *Science* 238(4830):1098-104 (1987). 25 Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody.

In another embodiment, the antibody may be conjugated 30 to a "receptor" (such as streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of

unbound conjugate from the circulation using a clearing agent, and then administration of a "ligand" (e.g., avidin) which is conjugated to a cytotoxic agent (e.g., a radionucleotide).

5 The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Eppstein, et al., *Proc. Natl. Acad. Sci. USA* 82:3688-92 (1985); Hwang, et al., *Proc. Natl. Acad. Sci. USA* 10 77(7):4030-4 (1980); and U.S. Patents 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent 5,013,556.

Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition 15 comprising phosphatidylcholine, cholesterol and PEG- derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the 20 liposomes as described in Martin, et al., *J. Biol. Chem.* 257(1):286-8 (1982) via a disulfide interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon, et al., *J. National Cancer Inst.* 81(19):484-8 (1989).

25 Antibodies specifically binding an LP polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders in the form of pharmaceutical compositions.

30 If an LP polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also

be used to deliver the antibody or an antibody fragment into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For 5 example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, e.g., Marasco, et al., 10 *Proc. Natl. Acad. Sci. USA* 90(16):7889-93 (1993).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other.

15 Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokines, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitable present in combination in amounts that are effective for 20 the purpose intended. The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, 25 respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition (1980).

30 The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol), polylactides (U.S. Patent 3,773,919), copolymers of L-glutamic acid gamma-ethyl-L-glutamate, non-degradable ethylene-vinylacetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)3-hydroxylbutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37 degrees C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanisms involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thiosulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

The anti-LP polypeptide antibodies of the present invention have various utilities. For example, such antibodies may be used in diagnostic assays for LP

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polypeptide expression, e.g., detecting expression in specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases [Zola, *Monoclonal Antibodies: A Manual of Techniques*, CRC Press, Inc., pp. 147-158 (1987)]. The antibodies used in the assays can be labeled with a detectable moiety. The detectable moiety should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I , a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase. Any method known in the art for conjugating the antibody to the detectable moiety may be employed, including those methods described by Hunter, et al., *Nature* 144:945 (1962); David, et al., *Biochemistry* 13(5):1014-21 (1974); Pain, et al., *J. Immunol. Meth.*, 40(2):219-30 (1981); and Nygren, *J. Histochem. Cytochem.* 30(5):407-12 (1982).

Anti-LP polypeptide antibodies also are useful for affinity purification from recombinant cell culture or natural sources. In this process, the antibodies are immobilized on a suitable support, such as a Sephadex[®] resin or filter paper, using methods well known in the art. The immobilized antibody is then contacted with a sample containing the LP polypeptide to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the LP polypeptide, which is bound to the

immobilized antibody. Finally, the support is washed with another suitable solvent that will release the desired polypeptide from the antibody.

This invention encompasses methods of screening 5 compounds to identify those that mimic the activity of the LP polypeptide (agonists) disclosed herein or prevent the effects of the LP polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identity compounds that bind or complex with an LP 10 polypeptide encoded by the genes identified herein or otherwise interfere with the interaction of LP polypeptides with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for 15 identifying small molecule drug candidates.

The assays can be performed in a variety of formats. In binding assays, the interaction is binding, and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, an LP polypeptide 20 encoded by a gene identified herein or the drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution comprising LP polypeptide 25 and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to 30 the immobilized component, e.g., the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, e.g., by

washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing 5 occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not 10 bind to an LP polypeptide, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification 15 through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co- 20 workers [Fields and Song, *Nature* 340(6230):245-6 (1989); Chien, et al., *Proc. Natl. Acad. Sci. USA* 88(21):9578-82 (1991); Chevray and Nathans, *Proc. Natl. Acad. Sci. USA* 89(13):5789-93 (1992)]. Many transcriptional activators, such as yeast GAL4, consist of two physically discrete 25 modular domains, one acting as the DNA-binding domain, while the other functions as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and 30 employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another in which candidate activating proteins are fused to

the activation domain. The expression of GAL1-lacZ reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting 5 polypeptides are detected with chromogenic substrate for beta-galactosidase. A complete kit (MATCHMAKERTM) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also 10 be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of an LP polypeptide identified herein and other intra- or 15 extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a 20 candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture to serve as a positive control. The binding (complex formation) between the test compound and the 25 intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test 30 compound and its reaction partner.

Antagonists may be detected by combining at least one LP polypeptide and a potential antagonist with a membrane-

bound or recombinant receptor for that LP polypeptide under appropriate conditions for a competitive inhibition assay. The LP polypeptide can be labeled, such as by radioactivity, such that the number of LP polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor for an LP polypeptide can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. See 10 Coligan, et al., *Current Protocols in Immunology* 1(2):Ch. 5 (1991). Preferably, expression cloning is employed such that polyadenylated mRNA is prepared from a cell responsive to the secreted form of a particular LP polypeptide, and a cDNA library created from this mRNA is divided into pools 15 and used to transfect COS cells or other cells that are not responsive to the secreted LP polypeptide. Transfected cells that are grown on glass slides are exposed to the labeled LP polypeptide. The LP polypeptide can be labeled by a variety of means including iodination or inclusion of 20 a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, 25 eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, a labeled LP polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the 30 receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into

peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify 5 the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with a labeled LP polypeptide in the presence of the candidate compound. The ability of the compound to 10 enhance or block this interaction could then be removed.

Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the LP polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the 15 polypeptide.

Another potential LP antagonist is an anti-sense RNA or DNA construct prepared using anti-sense technology, where, e.g., an anti-sense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to 20 targeted mRNA and prevent its translation into protein. Anti-sense technology can be used to control gene expression through triple-helix formation or anti-sense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding 25 portion of the polynucleotide sequence, which encodes the mature form of an LP polypeptide can be used to design an anti-sense RNA oligonucleotide sequence of about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in 30 transcription [triple helix; see Lee, et al., *Nucl. Acids Res* 6(9):3073-91 (1979); Cooney, et al., *Science* 241(4864):456-9 (1988); Beal and Dervan, *Science*

251(4999):1360-3 (1991)], thereby preventing transcription and production of the LP polypeptide. The anti-sense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecules [anti-sense; see Okano, 5 *J. Neurochem.* 56(2):560-7 (1991); *Oligodeoxynucleotides as Anti-sense Inhibitors of Gene Expression* (CRC Press: Boca Raton, FL 1988)]. The oligonucleotides described above can also be delivered to cells such that the anti-sense RNA or DNA may be expressed *in vivo* to inhibit production of the 10 LP polypeptide. When anti-sense DNA is used, oligodeoxy-ribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that 15 bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the LP polypeptide, thereby blocking the normal biological activity of the LP polypeptide. Examples of small molecules include, but are not limited to, small peptides 20 or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target 25 RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details, see, e.g., Rossi, *Current Biology* 4(5):469-71 (1994) and PCT publication No. WO 97/33551 (published September 18, 30 1997).

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and

composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or 5 pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

Another use of the compounds of the invention (e.g., LP polypeptides, fragments and variants thereof and LP antibodies directed thereto) described herein is to help 10 diagnose whether a disorder is driven to some extent by the modulation of signaling by an LP polypeptide

A diagnostic assay to determine whether a particular disorder is driven by LP polypeptide dependent signaling can be carried out using the following steps:

- 15 a) culturing test cells or tissues expressing an LP polypeptide;
- b) administering a compound which can inhibit LP polypeptide dependent signaling; and
- c) measuring LP polypeptide mediated phenotypic effects

20 in the test cells.

The steps can be carried out using standard techniques in light of the present disclosure. Appropriate controls take into account the possible cytotoxic effect of a compound, such as treating cells not associated with a cell 25 proliferative disorder (e.g., control cells) with a test compound and can also be used as part of the diagnostic assay. The diagnostic methods of the invention involve the screening for agents that modulate the effects of LP polypeptide-associated disorders.

30 The LP polypeptides or antibodies thereto as well as LP polypeptide antagonists or agonists can be employed as therapeutic agents. Such therapeutic agents are formulated

according to known methods to prepare pharmaceutically useful compositions, whereby the LP polypeptide or antagonist or agonist thereof is combined in a mixture with a pharmaceutically acceptable carrier.

5 In the case of LP polypeptide antagonistic or agonistic antibodies, if the LP polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the
10 antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment which specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable region sequences of an antibody, peptide
15 molecules can be designed which retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology [see, e.g., Marasco, et al., *Proc. Natl. Acad. Sci. USA* 90(16):7889-93 (1993)].

20 Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers [*Remington's Pharmaceutical Sciences* 16th edition (1980)], in the form of lyophilized
25 formulations or aqueous solutions.

 The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Such
30 molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-
5 (methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences, supra*.

10 The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

15 Therapeutic compositions herein generally are placed into a container having a sterile access port, for example, and intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

20 Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent(s), which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels [for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)], polylactides, copolymers of L-
25 glutamic acid and gamma-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOTTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-
30 hydroxybutyric acid. Microencapsulation of recombinant proteins for sustained release has been successfully performed with human growth hormone (rhGH), interferon, and

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interleukin-2. Johnson, et al., *Nat. Med.* 2(7):795-9 (1996); Yasuda, et al., *Biomed. Ther.* 27:1221-3 (1993);

Hora, et al., *Bio/Technology* 8(8):755-8 (1990); Cleland, "Design and Production of Single Immunization Vaccines

5 Using Polylactide Polyglycolide Microsphere Systems" in *Vaccine Design: The Subunit and Adjuvant Approach*, Powell and Newman, Eds., Plenum Press, NY, 1995, pp. 439-462 WO 97/03692; WO 96/40072; WO 96/07399; and U.S. Patent 5,654,010.

10 The sustained-release formulations of these proteins may be developed using polylactic-glycolic acid (PLGA) polymer due to its biocompatibility and wide range of biodegradable properties. The degradation products of PLGA, lactic and glycolic acids, can be cleared quickly 15 within the human body. Moreover, the degradability of this polymer can be adjusted from months to years depending on its molecular weight and composition. See Lewis, "Controlled release of bioactive agents from lactide/glycolide polymer" in *Biodegradable Polymers as 20 Drug Delivery Systems* (Marcel Dekker; New York, 1990), M. Chasin and R. Langer (Eds.) pp. 1-41.

While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for 25 shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37 degrees C, resulting in a loss of biological activity and possible changes in immunogenicity.

30 It is contemplated that the compounds, including, but not limited to, antibodies, small organic and inorganic molecules, peptides, anti-sense molecules, ribozymes, etc.,

of the present invention may be used to treat various conditions including those characterized by overexpression and/or activation of the disease-associated genes identified herein. The active agents of the present

5 invention (e.g., antibodies, polypeptides, nucleic acids, ribozymes, small organic or inorganic molecules) are administered to a mammal, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by
10 intramuscular, intraperitoneal, intracerebral, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, intraocular, intralesional, oral, topical, inhalation, pulmonary, and/or through sustained release.

15 Other therapeutic regimens may be combined with the administration of LP polypeptide antagonists or antagonists, anti-cancer agents, e.g., antibodies of the instant invention.

For the prevention or treatment of disease, the
20 appropriate dosage of an active agent, (e.g., an antibody, polypeptide, nucleic acid, ribozyme, or small organic or inorganic molecule) will depend on the type of disease to be treated, as defined above, the severity and course of the disease, whether the agent is administered for
25 preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the agent, and the discretion of the attending physician. The agent is suitably administered to the patient at one time or over a series of treatments.

30 Dosages and desired drug concentration of pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. The

determination of the appropriate dosage or route of administration is well within the skill of an ordinary artisan. Animal experiments provide reliable guidance for the determination of effective doses for human therapy.

5 Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti and Chappell, "The Use of Interspecies Scaling in Toxicokinetics," in *Toxicokinetics and New Drug Development*, Yacobi, et al., Eds., Pergamon Press, NY,
10 p.4246 (1989).

When *in vivo* administration of a composition comprising an LP polypeptide, an LP polypeptide antibody, an LP polypeptide-encoding nucleic acid, ribozyme, or small organic or inorganic molecule is employed, normal dosage amounts may vary from about 1 ng/kg up to 100 mg/kg of mammal body weight or more per day, preferably about 1 pg/kg/day up to 100 mg/kg of mammal body weight or more per day, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature; see, for example, U.S. Patents 4,657,760, 5,206,344 or 5,225,212. It is within the scope of the invention that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue. Moreover, dosages may be administered by one or more separate administrations or by continuous infusion. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress

of this therapy is easily monitored by conventional techniques and assays.

In another embodiment of the invention, an article of manufacture containing materials useful for the diagnosis or treatment of the disorders described above is provided. The article of manufacture comprises a container and a label. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for diagnosing or treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is typically an LP polypeptide, antagonist or agonist thereof. The label on, or associated with, the container indicates that the composition is used for diagnosing or treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

In another embodiment of the invention, therapeutic utility of the LP polypeptide is determined by measuring phosphorylation of tyrosine residues on specific cell lines. The early cellular response of cells stimulated with the majority of proteins is protein phosphorylation of the tyrosine residues. This response includes autophosphorylation of corresponding receptors, which thereby leads

to the activation of catalytic properties and the initiation of intracellular pathways specific to the cell type. Moreover, signaling downstream of receptors requires phosphorylation of specific kinases inside the cell and 5 other intracellular enzymes of different origin as well as the phosphorylation of multiple adapter/scaffold, structural proteins and transcriptional factors. Therefore, diverse protein-induced cell responses can be visualized by monitoring the state of protein 10 phosphorylation after cell stimulation.

Immunodetection is used to detect the protein phosphorylation of the stimulated cell. Several antibodies that are directed against specific phosphorylated epitopes in signaling molecules are readily available. Two specific 15 antibodies are used: phosphospecific anti-MAPK and anti-AKT antibodies. Additionally, non-specific anti-phosphotyrosine antibodies, which recognize tyrosine-phosphorylated proteins, are used. While anti-phosphotyrosine antibodies allow detection of diverse tyrosine phosphorylated proteins 20 without directly addressing the nature of their identity, the phosphospecific anti-MAPK and anti-AKT antibodies recognize only the corresponding proteins in their phosphorylated form.

Another assay to determine utility of LP polypeptides 25 involves transfection of cell lines with reporter plasmids followed by cell stimulation with an LP polypeptide. Each reporter consists of a defined element, responsive to specific intracellular signaling pathways, upstream of a sequence involving a reporter protein such as luciferase. 30 Upon stimulation of the element, reporter transcription and translation ensues, and the resulting protein levels can be detected using an assay such as a luminescence assay. The

cell stimulation period depends on the reporter plasmid used.

For each reporter used, positive controls are designed in the form of agonist cocktails which include approximately 5 maximal stimulatory doses of several ligands known to stimulate the represented signaling pathway. Using this design, the chances of finding a positive stimulus for each cell line is maximized. The caveat, however, is that some cell line / reporter combinations will not be stimulated by 10 the specific agonist cocktail, due to lack of an appropriate ligand in the cocktail. Alternately, the lack of signal induction by an agonist cocktail may be the lack of all 15 signaling components within a particular cell line to activate the transcriptional element. Cell line / reporter combinations with no exogenous stimulus added make up the negative controls.

Another assay to determine utility of LP polypeptides involves transfection of cell lines with reporter plasmids followed by cell stimulation with an LP polypeptide. Each 20 reporter consists of a defined element, responsive to specific intracellular signaling pathways, upstream of a sequence involving a reporter protein such as luciferase. Upon stimulation of the element, reporter transcription and 25 translation ensues, and the resulting protein levels can be detected using an assay such as a luminescence assay. The cell stimulation period depends on the reporter plasmid used.

For each reporter used, positive controls are designed in the form of agonist cocktails which include 30 approximately maximal stimulatory doses of several ligands known to stimulate the represented signaling pathway. Using this design, the chances of finding a positive

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stimulus for each cell line is maximized. The caveat, however, is that some cell line/reporter combinations will not be stimulated by the specific agonist cocktail, due to lack of an appropriate ligand in the cocktail.

5 Alternately, the lack of signal induction by an agonist cocktail may be the lack of all signaling components within a particular cell line to activate the transcriptional element. Cell line / reporter combinations with no exogenous stimulus added make up the negative controls.

10 In another assay, utility of LP polypeptide is determined by proliferation of cells. In this assay, gross changes in the number of cells remaining in a culture are monitored after exposure to an LP polypeptide for three days. The cells are incubated in an appropriate assay
15 medium to produce a sub-optimal growth rate. For example, usually a 1:10 or 1:20 dilution of normal culture medium results in a 40 to 60% reduction in cell number compared to the undiluted culture medium. This broad growth zone is chosen so that if an LP polypeptide is a stimulator of
20 growth, the cells have room to expand, and conversely, if the LP polypeptide is deleterious, a reduction in cell density can be detected. After a period of exposure, the assay media is replaced with media containing a detection agent such as Calcein AM, a membrane-permeant fluorescent
25 dye, allowing quantification of the cell number.

For use in another assay, a FLAG-HIS (FLIS)-tagged version of the LP polypeptide is expressed using mammalian cells such as HEK-293EBNA, COS-7, or HEK293T. The coding region of the cDNA is amplified by PCR of a vector
30 containing a fragment encoding the LP polypeptide. The PCR-generated fragment is cleaved with restriction enzymes and gel-purified. The fragment is then ligated into a

mammalian expression vector containing the FLIS epitope tag fused to the C-terminus. Protein expressed by this plasmid construct includes both the FLAG tag (Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys) and the 6X His tag at the COOH -terminus of 5 the protein. This tag provides epitopes for commercially available tag-specific antibodies, enabling detection of the protein.

To determine expression of the LP polypeptide in tissues, a protein-binding assay is performed. The fixed 10 tissue sample is exposed to the FLIS-tagged LP polypeptide, followed by exposure to a primary antibody and a secondary antibody containing a fluorescent dye. Tagged LP polypeptide that binds to the antigens in the tissue will fluoresce. Binding of the protein to an antigen in the 15 tissue suggests that the protein is expressed in that tissue. Thus, protein expression can be determined by measuring which tissues fluoresce.

Having generally described the invention, the same will be more readily understood by reference to the 20 following examples, which are provided by way of illustration and are not intended as limiting.

EXAMPLES

Example 1

25 Expression and Purification of LP polypeptides in *E. coli*

The bacterial expression vector pQE60 is used for bacterial expression in this example. (QIAGEN, Inc., Chatsworth, CA). pQE60 encodes ampicillin antibiotic resistance ("Ampr") and contains a bacterial origin of 30 replication ("ori"), an IPTG inducible promoter, a ribosome binding site ("RBS"), six codons encoding histidine residues that allow affinity purification using nickel-nitrilo-

triacetic acid ("Ni-NTA") affinity resin sold by QIAGEN, Inc., and suitable single restriction enzyme cleavage sites. These elements are arranged such that a DNA fragment encoding a polypeptide can be inserted in such a way as to 5 produce that polypeptide with the six His residues (i.e., a "6 X His tag") covalently linked to the carboxyl terminus of that polypeptide. However, a polypeptide coding sequence can optionally be inserted such that translation of the six His codons is prevented and, therefore, a polypeptide is 10 produced with no 6 X His tag.

The nucleic acid sequence encoding the desired portion of an LP polypeptide lacking the hydrophobic leader sequence is amplified from a cDNA clone using PCR oligonucleotide primers (based on the sequences presented, e.g., in SEQ ID 15 NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37) which anneal to the amino terminal encoding DNA sequences of the desired portion of the LP polypeptide-encoding nucleic acid and to sequences in the construct 3' to the cDNA coding sequence. Additional 20 nucleotides containing restriction sites to facilitate cloning in the pQE60 vector are added to the 5' and 3' sequences, respectively.

For cloning, the 5' and 3' primers have nucleotides corresponding or complementary to a portion of the coding 25 sequence of the LP polypeptide-encoding nucleic acid, e.g., as presented in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37, according to known method steps. One of ordinary skill in the art would appreciate, of course, that the point in a polynucleotide 30 sequence where the 5' primer begins can be varied to amplify a desired portion of the complete polypeptide-encoding

polynucleotide shorter or longer than the polynucleotide which encodes the mature form of the polypeptide.

The amplified nucleic acid fragments and the vector pQE60 are digested with appropriate restriction enzymes, and 5 the digested DNAs are then ligated together. Insertion of the LP polypeptide-encoding DNA into the restricted pQE60 vector places the LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), or 10 LP223(b) polypeptide coding region including its associated stop codon downstream from the IPTG-inducible promoter and in-frame with an initiating AUG codon. The associated stop codon prevents translation of the six histidine codons downstream of the insertion point.

15 The ligation mixture is transformed into competent *E. coli* cells using standard procedures such as those described in Sambrook, et al., 1989; Ausubel, 1987-1998. *E. coli* strain M15/rep4, containing multiple copies of the plasmid pREP4, which expresses the lac repressor and confers 20 kanamycin resistance ("Kanr"), is used in carrying out the illustrative example described herein. This strain, which is only one of many that are suitable for expressing LP polypeptides, is available commercially from QIAGEN, Inc. Transformants are identified by their ability to grow on LB 25 plates in the presence of ampicillin and kanamycin. Plasmid DNA is isolated from resistant colonies and the identity of the cloned DNA confirmed by restriction analysis, PCR and DNA sequencing.

Clones containing the desired constructs are grown 30 overnight ("O/N") in liquid culture in LB media supplemented with both ampicillin (100 μ g/mL) and kanamycin (25 μ g/mL). The O/N culture is used to inoculate a large

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culture, at a dilution of approximately 1:25 to 1:250. The cells are grown to an optical density at 600 nm ("OD600") of between 0.4 and 0.6. Isopropyl-beta-D-thiogalactopyranoside ("IPTG") is then added to a final concentration 5 of 1 mM to induce transcription from the lac repressor sensitive promoter, by inactivating the lacI repressor. Cells subsequently are incubated further for three to four hours. Cells then are harvested by centrifugation.

The cells are then stirred for three to four hours at 10 4 degrees C in 6 M guanidine hydrochloride, pH 8. The cell debris is removed by centrifugation, and the supernatant containing the LP polypeptide is dialyzed against 50 mM sodium acetate buffer, pH 6, supplemented with 200 mM sodium chloride. Alternatively, a polypeptide can be 15 successfully refolded by dialyzing it against 500 mM sodium chloride, 20% glycerol, 25 mM Tris hydrochloride, pH 7.4, containing protease inhibitors.

If insoluble protein is generated, the protein is made 20 soluble according to known method steps. After renaturation, the polypeptide is purified by ion exchange, hydrophobic interaction, and size exclusion chromatography. Alternatively, an affinity chromatography step such as an antibody column is used to obtain pure LP polypeptide. The purified polypeptide is stored at 4 degrees C or frozen at 25 negative 40 degrees C to negative 120 degrees C.

Example 2

Cloning and Expression of LP polypeptides in a Baculovirus Expression System

30 In this example, the plasmid shuttle vector pA2 GP is used to insert the cloned DNA encoding the mature LP polypeptide into a baculovirus, using a baculovirus leader

and standard methods as described in Summers, et al., *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agricultural Experimental Station Bulletin No. 1555 (1987). This expression vector contains 5 the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by the secretory signal peptide (leader) of the baculovirus gp67 polypeptide and convenient restriction sites such as BamHI, Xba I, and Asp718. The polyadenylation site of the simian 10 virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the 15 polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate viable virus that expresses the cloned polynucleotide.

Other baculovirus vectors are used in place of the 20 vector above, such as pAc373, pVL941 and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. 25 Such vectors are described, for instance, in Luckow, et al., *Virology* 170:31-39.

The cDNA sequence encoding the mature LP polypeptide in a clone, lacking the AUG initiation codon and the naturally associated nucleotide binding site, is amplified using PCR 30 oligonucleotide primers corresponding to the 5' and 3' sequences of the gene. Non-limiting examples include 5' and 3' primers having nucleotides corresponding or complementary

to a portion of the coding sequence of an LP polypeptide-encoding polynucleotide, e.g., as presented in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37 according to known method steps.

5 The amplified fragment is isolated from a 1% agarose gel using a commercially available kit (e.g., "Geneclean," BIO 101 Inc., La Jolla, CA). The fragment is then digested with the appropriate restriction enzyme and again is purified on a 1% agarose gel. This fragment is designated
10 herein "F1."

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, CA). This vector DNA is designated herein "V1."

Fragment F1 and the dephosphorylated plasmid V1 are ligated together with T4 DNA ligase. *E. coli* HB101 or other
20 suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria are identified that contain the plasmid bearing a human LP polypeptide-encoding polynucleotide using the PCR method, in
25 which one of the primers that is used to amplify the gene and the second primer is from well within the vector so that only those bacterial colonies containing an LP polypeptide-encoding polynucleotide will show amplification of the DNA. The sequence of the cloned fragment is confirmed by DNA
30 sequencing. The resulting plasmid is designated herein as pBacLP.

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Five μ g of the plasmid pBacLP plasmid construct is co-transfected with 1.0 μ g of a commercially available linearized baculovirus DNA ("BaculoGold[®] baculovirus DNA", PharMingen, San Diego, CA), using the lipofection method 5 described by Felgner, et al., *Proc. Natl. Acad. Sci. USA* 84: 7413-7 (1987). 1 μ g of BaculoGold[®] virus DNA and 5 μ g of the plasmid pBacLP are mixed in a sterile well of a microtiter plate containing 50 μ L of serum-free Grace's medium (Life Technologies, Inc., Rockville, MD).

10 Afterwards, 10 μ L Lipofectin plus 90 μ L Grace's medium are added, mixed and incubated for fifteen minutes at room temperature. Then, the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 mL Grace's medium without 15 serum. The plate is rocked back and forth to mix the newly added solution. The plate is then incubated for five hours at 27 degrees C. After five hours, the transfection solution is removed from the plate and 1 mL of Grace's insect medium supplemented with 10% fetal calf serum is 20 added. The plate is put back into an incubator and cultivation is continued at 27 degrees C for four days.

After four days, the supernatant is collected, and a plaque assay is performed. An agarose gel with "Blue Gal" (Life Technologies, Inc., Rockville, MD) is used to allow 25 easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies, Inc., Rockville, MD, pp. 9-10). After appropriate incubation, 30 blue stained plaques are picked with a micropipettor tip (e.g., Eppendorf). The agar containing the recombinant

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viruses is then resuspended in a microcentrifuge tube containing 200 μ L of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later, the 5 supernatants of these culture dishes are harvested and then stored at 4 degrees C.

To verify the expression of the LP polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the 10 recombinant baculovirus at a multiplicity of infection ("MOI") of about two. Six hours later, the medium is removed and replaced with SF900 II medium minus methionine and cysteine (available, e.g., from Life Technologies, Inc., Rockville, MD). If radiolabeled polypeptides are desired, 15 42 hours later, 5 mCi of 35 S-methionine and 5 mCi 35 S-cysteine (available from Amersham, Piscataway, NJ) are added. The cells are further incubated for sixteen hours and then harvested by centrifugation. The polypeptides in the supernatant as well as the intracellular polypeptides 20 are analyzed by SDS-PAGE, followed by autoradiography (if radiolabeled). Microsequencing of the amino acid sequence of the amino terminus of purified polypeptide can be used to determine the amino terminal sequence of the mature polypeptide and, thus, the cleavage point and length of the 25 secretory signal peptide.

Example 3

Cloning and Expression of an LP Polypeptide in Mammalian Cells

30 A typical mammalian expression vector contains at least one promoter element, which mediates the initiation

of transcription of mRNA, the polypeptide coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening 5 sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription can be achieved with the early and late promoters from SV40, the long terminal repeats (LTRS) from Retroviruses, e.g., RSV, HTLV, HIVI and the early promoter of the cytomegalovirus 10 (CMV). However, cellular elements can also be used (e.g., the human actin promoter). Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pIRES1neo, pRetro-Off, pRetro-On, PLXSN, or pLNCX (Clontech Labs, Palo Alto, CA), pcDNA3.1 15 (+/-), pcDNA/Zeo (+/-) or pcDNA3.1/Hygro (+/-) (Invitrogen), PSVL and PMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146) and pBC12MI (ATCC 67109). Other suitable mammalian host cells include human Hela 293, H9, Jurkat cells, mouse NIH3T3, C127 cells, 20 Cos 1, Cos 7 and CV 1, quail QC1-3 cells, mouse L cells, and Chinese hamster ovary (CHO) cells.

Alternatively, the gene is expressed in stable cell lines that contain the gene integrated into a chromosome. The co-transfection with a selectable marker such as DHFR 25 (dihydrofolate reductase), GPT neomycin, or hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded polypeptide. The DHFR marker 30 is useful to develop cell lines that carry several hundred or even several thousand copies of the gene of interest. Another useful selection marker is the enzyme glutamine

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synthase (GS) [Murphy, et al., *Biochem. J.* 227:277-9 (1991); Bebbington, et al., *Bio/Technology* 10:169-75 (1992)]. Using these markers, the mammalian cells are grown in selective medium and the cells with the highest 5 resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NS0 cells are often used for the production of polypeptides.

The expression vectors pC1 and pC4 contain the strong 10 promoter (LTR) of the Rous Sarcoma Virus [Cullen, et al., *Mol. Cell. Biol.* 5:438-47 (1985)] plus a fragment of the CMV-enhancer [Boshart, et al., *Cell* 41:521-30 (1985)]. Multiple cloning sites, e.g., with the restriction enzyme 15 cleavage sites BamHI, XbaI, and Asp718, facilitate the cloning of the gene of interest. The vectors contain in addition the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene.

Example 3(a)

20 Cloning and Expression in COS Cells

The expression plasmid, pLP HA, is made by cloning a cDNA encoding LP polypeptide into the expression vector pcDNAI/Amp or pcDNAIII (which can be obtained from Invitrogen, Inc.).

25 The expression vector pcDNAI/amp contains: (1) an *E. coli* origin of replication effective for propagation in *E. coli* and other prokaryotic cells; (2) an ampicillin resistance gene for selection of plasmid-containing prokaryotic cells; (3) an SV40 origin of replication for propagation in eukaryotic cells; (4) a CMV promoter, a polylinker, an SV40 intron; (5) several codons encoding a hemagglutinin fragment (i.e., an "HA" tag to facilitate 30

purification) or HIS tag (see, e.g., Ausubel, *supra*) followed by a termination codon and polyadenylation signal arranged so that a cDNA can be conveniently placed under expression control of the CMV promoter and operably linked 5 to the SV40 intron and the polyadenylation signal by means of restriction sites in the polylinker. The HA tag corresponds to an epitope derived from the influenza hemagglutinin polypeptide described by Wilson, et al., *Cell* 37:767-8 (1984). The fusion of the HA tag to the target 10 polypeptide allows easy detection and recovery of the recombinant polypeptide with an antibody that recognizes the HA epitope. pcDNAIII contains, in addition, the selectable neomycin marker.

A DNA fragment encoding the LP polypeptide is cloned 15 into the polylinker region of the vector so that recombinant polypeptide expression is directed by the CMV promoter. The plasmid construction strategy is as follows. The LP polypeptide-encoding cDNA of a clone is amplified using primers that contain convenient restriction sites, 20 much as described above for construction of vectors for expression of LP polypeptides in *E. coli*. Non-limiting examples of suitable primers include those based on the coding sequences presented in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37.

25 The PCR amplified DNA fragment and the vector, pcDNAI/Amp, are digested with suitable restriction enzyme(s) and then ligated. The ligation mixture is transformed into *E. coli* strain SURE (available from Stratagene Cloning Systems, La Jolla, CA), and the 30 transformed culture is plated on ampicillin media plates which then are incubated to allow growth of ampicillin resistant colonies. Plasmid DNA is isolated from resistant

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colonies and examined by restriction analysis or other means for the presence of the LP polypeptide-encoding fragment.

For expression of recombinant LP polypeptide, COS 5 cells are transfected with an expression vector, as described above, using DEAE-DEXTRAN, as described, for instance, in Sambrook, et al., *Molecular Cloning: a Laboratory Manual*, Cold Spring Laboratory Press, Cold Spring Harbor, New York (1989). Cells are incubated under 10 conditions for expression of the LP polypeptide-encoding polynucleotide by the vector.

Expression of the LP polypeptide-HA fusion is detected by radiolabeling and immunoprecipitation, using methods described in, for example Harlow, et al., *Antibodies: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (1988). To this end, two days after transfection, the cells are labeled by incubation in media containing 35 S-cysteine for eight hours. The cells and the media are collected, and the cells are 20 washed and lysed with detergent-containing RIPA buffer: 150 mM sodium chloride, 1% NP-40, 0.1% SDS, 0.5% DOC, 50 mM TRIS, pH 7.5, as described by Wilson, et al., cited above. Proteins are precipitated from the cell lysate and from the culture media using an HA-specific monoclonal antibody. 25 The precipitated polypeptides then are analyzed by SDS-PAGE and autoradiography. An expression product of the expected size is seen in the cell lysate, which is not seen in negative controls.

Example 3 (b)Cloning and Expression in CHO Cells

The vector pC4 is used for the expression of the LP polypeptide. Plasmid pC4 is a derivative of the plasmid 5 pSV2-dhfr (ATCC Accession No. 37146). The plasmid contains the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary cells or other cells lacking dihydrofolate activity that are transfected with these plasmids can be selected by growing the cells in a 10 selective medium (alpha minus MEM, Life Technologies) supplemented with methotrexate. The amplification of the DHFR genes in cells resistant to methotrexate (MTX) has been well documented [see, e.g., Alt, et al., *J. Biol. Chem.* 253:1357-70 (1978); Hamlin and Ma, *Biochem. et 15 Biophys. Acta* 1097:107-43 (1990); and Page and Sydenham, *Biotechnology* 9:64-8 (1991)]. Cells grown in increasing concentrations of MTX develop resistance to the drug by overproducing the target enzyme, DHFR, as a result of amplification of the DHFR gene. If a second gene is linked 20 to the DHFR gene, it is usually co-amplified and over-expressed. It is known in the art that this approach can be used to develop cell lines carrying more than 1,000 copies of the amplified gene(s). Subsequently, when the methotrexate is withdrawn, cell lines are obtained which 25 contain the amplified gene integrated into one or more chromosome(s) of the host cell.

Plasmid pC4 contains for expressing the gene of interest the strong promoter of the long terminal repeat (LTR) of the Rous Sarcoma Virus [Cullen, et al., *Mol. Cell. Biol.* 5: 438-47 (1985)] plus a fragment isolated from the 30 enhancer of the immediate early gene of human cytomegalovirus (CMV) [Boshart, et al., *Cell* 41: 521-30 (1985)].

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Downstream of the promoter are BamHI, XbaI, and Asp718 restriction enzyme cleavage sites that allow integration of the genes. Behind these cloning sites, the plasmid contains the 3' intron and polyadenylation site of the rat 5 preproinsulin gene. Other high efficiency promoters can also be used for the expression, e.g., the human beta-actin promoter, the SV40 early or late promoters or the long terminal repeats from other retroviruses, e.g., HIV and HTLV. Clontech's Tet-Off and Tet-On gene expression 10 systems and similar systems can be used to express the LP polypeptide in a regulated way in mammalian cells [Gossen, and Bujard, *Proc. Natl. Acad. Sci. USA* 89:5547-51 (1992)]. For the polyadenylation of the mRNA other signals, e.g., from the human growth hormone or globin genes can be used 15 as well. Stable cell lines carrying a gene of interest integrated into the chromosomes can also be selected upon co-transfection with a selectable marker such as gpt, G418 or hygromycin. It is advantageous to use more than one selectable marker in the beginning, e.g., G418 plus 20 methotrexate.

The plasmid pC4 is digested with restriction enzymes and then dephosphorylated using calf intestinal phosphatase by procedures known in the art. The vector is then isolated from a 1% agarose gel.

25 The DNA sequence encoding the complete the LP polypeptide is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene. Non-limiting examples include 5' and 3' primers having nucleotides corresponding or complementary to a portion of 30 the coding sequences of an LP polypeptide-encoding polynucleotide, e.g., as presented in SEQ ID NO:1, 3, 5, 7,

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9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37, according to known method steps.

The amplified fragment is digested with suitable endonucleases and then purified again on a 1% agarose gel.

5 The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC4 using, for instance, restriction enzyme analysis.

10 Chinese hamster ovary (CHO) cells lacking an active DHFR gene are used for transfection. Five μ g of the expression plasmid pC4 is cotransfected with 0.5 μ g of the plasmid pSV2-neo using lipofectin. The plasmid pSV2-neo contains a dominant selectable marker, the neo gene from

15 Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 μ g/mL G418. After two days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM

20 supplemented with 10, 25, or 50 ng/mL of methotrexate plus 1 μ g/mL G418. After about ten to fourteen days, single clones are trypsinized and then seeded in six-well petri dishes or 10 mL flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM).

25 Clones growing at the highest concentrations of methotrexate are then transferred to new six-well plates containing even higher concentrations of methotrexate (1 mM, 2 mM, 5 mM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a

30 concentration of 100 to 200 mM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

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Example 4

Tissue Distribution of LP polypeptide-encoding mRNA

Northern blot analysis is carried out to examine
5 expression of LP-polypeptide mRNA in human tissues, using
methods described by, among others, Sambrook, et al., cited
above. A cDNA preferably probe encoding the entire LP
10 polypeptide is labeled with ^{32}P using the Rediprime™ DNA
labeling system (Amersham Life Science), according to the
manufacturer's instructions. After labeling, the probe is
purified using a CHROMA SPIN-100™ column (Clontech
15 Laboratories, Inc.) according to the manufacturer's protocol
number PT1200-1. The purified and labeled probe is used to
examine various human tissues for LP polypeptide mRNA.

Multiple Tissue Northern (MTN) blots containing various
human tissues (H) or human immune system tissues (IM) are
obtained from Clontech and are examined with the labeled
probe using ExpressHyb™ hybridization solution (Clontech)
according to manufacturer's protocol number PT1190-1.
20 Following hybridization and washing, the blots are mounted,
exposed to film at negative 70 degrees C overnight, and
developed according to standard procedures.

Example 5

Protein Phosphorylation on Tyrosine Residues

Protein-induced cell responses are determined by
monitoring tyrosine phosphorylation upon stimulation of
cells by addition of LP polypeptides. This is accomplished
in two steps: cell manipulation and immunodetection.

30 Protein phosphorylation is measured using the SK-N-MC
neuroblastoma cell line (ATCC HTB-10). On day one, the
cells are plated into poly-D-lysine-coated, 96 well plates

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containing cell propagation medium [DMEM:F12 (3:1), 20 mM HEPES at pH 7.5, 5% FBS, and 50 µg/mL Gentamicin]. The cells are seeded at a concentration of 20,000 cells per well in 100 µL medium. On day two, the propagation medium in 5 each well is replaced with 100 µL starvation medium containing DMEM:F12 (3:1), 20 mM HEPES at pH 7.5, 0.5% FBS, and 50 µg/mL Gentamicin. The cells are incubated overnight.

On day three, pervanadate solution is made ten minutes before cell lysis; pervanadate is prepared by mixing 100 µL 10 of sodium orthovanadate (100 mM) and 3.4 µL of hydrogen peroxide (producing 100X stock pervanadate solution). The lysis buffer is then prepared: 50 mM HEPES at pH 7.5, 150 mM sodium chloride, 10% glycerol, 1% TRITON-X100™, 1 mM EDTA, 1 mM pervanadate, and BM protease inhibitors. The 15 cells are stimulated by adding 10 µL of the LP polypeptide solution to the cells, and incubating for ten minutes. Next, the medium is aspirated, and 75 µL lysis buffer are added to each well. The cells are lysed at 4 degrees C for fifteen minutes, then 25 µL of 4X loading buffer are added 20 to the cell lysates. The resultant solution is mixed then heated to 95 degrees C.

Detection of tyrosine phosphorylation is accomplished by Western immunoblotting. Twenty microliters of each cell sample are loaded onto SDS-PAGE eight to sixteen percent 25 amino acid-ready gels from Bio-Rad, and the gels are run. The proteins are electrotransferred in transfer buffer (25 mM Tris base at pH 8.3, 0.2 M glycine, 20% methanol) from the gel to a nitrocellulose membrane using 250 mA per gel over a one hour period. The membrane is incubated for 30 one hour at ambient conditions in blocking buffer consisting of TBST (20 mM Tris hydrochloride at pH 7.5, 150 mM sodium chloride, 0.1% TWEEN®-20) with 1% BSA.

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Next, the antibodies are added to the membrane. The membrane is incubated overnight at 4 degrees C with gentle rocking in primary antibody solution consisting of the antibody, TBST, and 1% BSA. The next day, the membrane is 5 washed three times, five minutes per wash, with TBST. The membrane is then incubated in the secondary antibody solution consisting of the antibody, TBST, and 1% BSA for one hour at ambient conditions with gentle rocking. After the incubation, the membrane is washed four times with 10 TBST, ten minutes per wash.

Detection is accomplished by incubating the membrane with 10 to 30 mL of SuperSignal Solution for one minute at ambient conditions. After one minute, excess developing solution is removed, and the membrane is wrapped in plastic 15 wrap. The membrane is exposed to X-ray film for twenty second, one minute, and two minute exposures (or longer if needed). The number and intensity of immunostained protein bands are compared to bands for the negative control-stimulated cells (basal level of phosphorylation) by visual 20 comparison.

LP251(a) stimulates phosphorylation in the SK-N-MC cell line and activates the AKT pathway.

Example 6

25 Cell Stimulation with Detection Utilizing Reporters

Protein-induced cell responses are measured using reporters. The SK-N-MC cell line (neuroblastoma; ATCC HTB-10) / NF κ B reporter combination is used.

For the reporter used, positive controls are designed 30 in the form of agonist cocktails. These cocktails include approximate maximal stimulatory doses of several ligands known to stimulate the regulated signal pathway. For the

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NFKB reporter, the NFKB / PkC pathway is stimulated by an agonist cocktail containing LPS and TNF-alpha as positive controls. Cell lines and reporters with no exogenous stimulus added are used as negative controls.

5 At time zero, the cells are transiently transfected with the reporter plasmids in tissue culture flasks using a standard optimized protocol for all cell lines (see Example 1). After 24 hours, the cells are trypsinized and seeded into 96-well poly-D-lysine coated assay plates at a rate of
10 20,000 cells per well in growth medium. After four to five hours, the medium is replaced with serum-free growth medium. At that time, stimulants for those reporters which required a 24-hour stimulation period are added. After 48 hours, stimulants for the reporters which required a five-hour
15 stimulation period are added. Five hours later, all conditions are lysed using a lysis/luciferin cocktail, and the fluorescence of the samples is determined using a Micro Beta reader.

Each assay plate is plated to contain four positive
20 control wells, sixteen negative control wells, and sixty-four test sample wells (two replicates of thirty-two test samples). The threshold value for a positive "hit" is a fluorescence signal equal to the mean plus two standard deviations of the negative control wells. Any test sample
25 that, in both replicates, generates a signal above that threshold is defined as a "hit."

LP240 stimulates the NFKB pathway of the neuroblastoma cell line SK-N-MC.

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Example 7

Cell Proliferation and Cytotoxicity Determination Utilizing
Fluorescence Detection

This assay is designed to monitor gross changes in the
5 number of cells remaining in culture after exposure to LP
polypeptides for a period of three days. The following
cells are used in this assay:

U373MG (astrocytoma cell line, ATCC HTB-22)
T1165 (plastocytoma cell line)
10 ECV304 endothelial cell line)

Prior to assay, cells are incubated in an appropriate
assay medium to produce a sub-optimal growth rate, e.g., a
1:10 or 1:20 dilution of normal culture medium. Cells are
15 grown in T-150 flasks, then harvested by trypsin digestion
and replated at 40 to 50% confluence into poly-D-lysine-
treated 96-well plates. Cells are only plated into the
inner thirty-two wells to prevent edge artifacts due to
medium evaporation; the outer wells are filled with buffer
20 alone. Following incubation overnight to stabilize cell
recovery, LP polypeptides are added to the appropriate
wells. Each polypeptide is assayed in triplicate at two
different concentrations, 1X and 0.1X dilution in assay
medium. Two controls are also included on each assay plate:
25 assay medium and normal growth medium.

After approximately 72 hours of exposure, the plates
are processed to determine the number of viable cells.
Plates are spun to increase the attachment of cells to the
plate. The medium is then discarded, and 50 μ L of detection
30 buffer is added to each well. The detection buffer
consisted on MEM medium containing no phenol red (Gibco)
with calcein AM (Molecular Probes) and PLURONIC[®] F-127

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(Molecular Probes), each at a 1:2000 dilution. After incubating the plates in the dark at room temperature for thirty minutes, the fluorescence intensity of each well is measured using a Cytofluor 4000-plate reader (PerSeptive Biosystems). For a given cell type, the larger the fluorescence intensity, the greater the number of cells in the well. To determine the effects on cell growth from each plate, the intensity of each well containing cells stimulated with an LP polypeptide is subtracted from the intensity of the wells containing assay medium only (controls). Thus, a positive number indicated stimulation of cell growth; a negative number indicated a reduction in growth. Additionally, confidence limits at 95 and 90% are calculated from the mean results. Results lying outside the 95% confidence limit are scored as "definite hits." Results lying between the 95 and 90% confidence limits are scored as "maybes." The distinction between definite hits and maybes varied due to intraplate variability; thus, subjective scoring is used as a final determination for "hits."

20 LP251(a) stimulates the growth of T1165 cells and suppresses the growth of U373MG cells. LP240 stimulates the proliferation of the ECV304 endothelial cell line.

WE CLAIM:

1. Isolated nucleic acid comprising DNA having at least 90% sequence identity to a polynucleotide selected from the 5 group consisting of:

- (a) a polynucleotide having a nucleotide sequence as shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37;
- (b) a polynucleotide encoding a polypeptide having the amino acid sequence as shown in SEQ ID NO:2, 10, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38;
- (c) a polynucleotide encoding the mature form of a polypeptide having the amino acid sequence as shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38;
- (d) a polynucleotide fragment of a polynucleotide as in (a), (b), or (c); and
- (e) a polynucleotide having a nucleotide sequence which is complementary to the nucleotide sequence of a polynucleotide as in (a), (b), (c), or (d).

2. An isolated nucleic acid molecule encoding an 25 polypeptide comprising DNA that hybridizes to the complement of the nucleic acid sequence that encodes LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), LP223(b), or any fragment or variant thereof.

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3. The isolated nucleic acid molecule of claim 2, wherein hybridization occurs under stringent hybridization and wash conditions.

5 4. A vector comprising the nucleic acid molecule of any of Claims 1 to 3.

5. The vector of Claim 4, wherein said nucleic acid molecule is operably linked to control sequences recognized by 10 a host cell transformed with the vector.

6. A host cell comprising the vector of Claim 5.

7. A process for producing an LP polypeptide comprising 15 culturing the host cell of Claim 6 under conditions suitable for expression of said LP polypeptide and recovering said LP polypeptide from the cell culture.

8. An isolated polypeptide comprising an amino acid 20 sequence comprising about 90% sequence identity to a sequence of amino acid residues comprising LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), or LP223(b) as shown in SEQ ID NO:2, 4, 6, 8, 10, 25 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38, respectively.

9. An isolated polypeptide comprising a sequence of 30 amino acid residues selected from the group consisting of:
(a) SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38;

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- (b) fragments of (a) sufficient to provide a binding site for an LP polypeptide antibody; and
- (c) variants of (a) or (b).

5 10. An isolated polypeptide produced by the method of
Claim 7.

11. A chimeric molecule comprising an LP polypeptide fused to a heterologous amino acid sequence.

10 12. The chimeric molecule of Claim 11, wherein said heterologous amino acid sequence is an epitope tag sequence.

15 13. The chimeric molecule of Claim 12, wherein said heterologous amino acid sequence is an Fc region of an immunoglobulin.

14. An antibody which specifically binds to an LP polypeptide.

20 15. The antibody of Claim 14, where said antibody is a monoclonal antibody.

25 16. The antibody of Claim 15, wherein said antibody is selected from the group consisting of a humanized antibody and a human antibody.

30 17. A composition comprising a therapeutically effective amount of an active agent selected from the group consisting of:

- (a) an LP polypeptide;
- (b) an agonist to an LP polypeptide;

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- (c) an antagonist to an LP polypeptide;
- (d) an LP polypeptide antibody;
- (e) an anti-LP polypeptide-encoding mRNA specific ribozyme; and
- 5 (f) a polynucleotide as in Claim 1, in combination with a pharmaceutically acceptable carrier.

18. A method of treating a mammal suffering from a disease, condition, or disorder associated with aberrant 10 levels of an LP-polypeptide comprising administering a therapeutically effective amount of an LP polypeptide or LP polypeptide agonist.

19. A method of diagnosing a disease, condition, or 15 disorder associated with aberrant levels of an LP polypeptide by: (1) culturing test cells or tissues expressing LP polypeptide; (2) administering a compound which can inhibit LP polypeptide modulated signaling; and (3) measuring the LP polypeptide-mediated phenotypic effects in the test cells or 20 tissues.

20. An article of manufacture comprising a container, label and therapeutically effective amount of the composition of Claim 17.

25 21. Use of an LP polypeptide in the manufacture of a medicament for the treatment of a disease, condition, or disorder associated with aberrant levels of an LP polypeptide.

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| Ser Ser Trp Val Pro Arg Ile Val Pro Gly Asp Ile Ser Ser Leu Ser | |
| 30 35 40 | |
| ctg gta aat ggg acg ttt tca gaa atc aag gac cga atg ttt tcc cat | 595 |
| Leu Val Asn Gly Thr Phe Ser Glu Ile Lys Asp Arg Met Phe Ser His | |
| 45 50 55 60 | |
| ctg cct tct ctg cag ctg cta ttg ctg aat tct aac tca ttc acg atc | 643 |
| Leu Pro Ser Leu Gln Leu Leu Leu Asn Ser Asn Ser Phe Thr Ile | |
| 65 70 75 | |
| atc cgg gat gat gct ttt gct gga ctt ttt cat ctt gaa tac tac ctg ttc | 691 |
| Ile Arg Asp Asp Ala Phe Ala Gly Leu Phe His Leu Glu Tyr Leu Phe | |
| 80 85 90 | |
| att gaa ggg aac aaa ata gaa acc att tca aga aat gcc ttt cgt ggc | 739 |
| Ile Glu Gly Asn Lys Ile Glu Thr Ile Ser Arg Asn Ala Phe Arg Gly | |
| 95 100 105 | |

| | |
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| ctc cgt gac ctg act cac ctt tct ttg gcc aat aac cac ata aaa gca Leu Arg Asp Leu Thr His Leu Ser Leu Ala Asn Asn His Ile Lys Ala 110 115 120 | 787 |
| cta cca agg gat gtc ttc agt gat tta gac tct ctg att gaa cta gat Leu Pro Arg Asp Val Phe Ser Asp Leu Asp Ser Leu Ile Glu Leu Asp 125 130 135 140 | 835 |
| ttg agg ggt aat aaa ttt gaa tgt gac tgc aaa gcc aag tgg cta tac Leu Arg Gly Asn Lys Phe Glu Cys Asp Cys Lys Ala Lys Trp Leu Tyr 145 150 155 | 883 |
| ctg tgg ttg aag atg aca aat tcc acc gtt tct gat gtg ctg tgt att Leu Trp Leu Lys Met Thr Asn Ser Thr Val Ser Asp Val Leu Cys Ile 160 165 170 | 931 |
| ggt cca cca gag tat cag gaa aag aag cta aat gac gtg acc agc ttt Gly Pro Pro Glu Tyr Gln Glu Lys Lys Leu Asn Asp Val Thr Ser Phe 175 180 185 | 979 |
| gac tat gaa tgc aca act aca gat ttt gtt cat cag act tta ccc Asp Tyr Glu Cys Thr Thr Asp Phe Val Val His Gln Thr Leu Pro 190 195 200 | 1027 |
| tac cag tcg gtt tca gtg gat acg ttc aac tcc aag aac gat gtg tac Tyr Gln Ser Val Ser Val Asp Thr Phe Asn Ser Lys Asn Asp Val Tyr 205 210 215 220 | 1075 |
| gtg gcc atc gcg cag ccc agc atg gag aac tgc atg gtg ctg gag tgg Val Ala Ile Ala Gln Pro Ser Met Glu Asn Cys Met Val Leu Glu Trp 225 230 235 | 1123 |
| gac cac att gaa atg aat ttc cgg agc tat gac aac att aca ggt cag Asp His Ile Glu Met Asn Phe Arg Ser Tyr Asp Asn Ile Thr Gly Gln 240 245 250 | 1171 |
| tcc atc gtg ggc tgt aag gcc att ctc atc gat gat cag gtc ttt gtg Ser Ile Val Gly Cys Lys Ala Ile Leu Ile Asp Asp Gln Val Phe Val 255 260 265 | 1219 |
| gtg gta gcc cag ctc ttc ggt ggc tct cac att tac aaa tac gac gag Val Val Ala Gln Leu Phe Gly Gly Ser His Ile Tyr Lys Tyr Asp Glu 270 275 280 | 1267 |
| agt tgg acc aaa ttt gtc aaa ttc caa gac ata gag gtc tct cgc att Ser Trp Thr Lys Phe Val Lys Phe Gln Asp Ile Glu Val Ser Arg Ile 285 290 295 300 | 1315 |
| tcc aag ccc aat gac atc gag ctg ttt cag atc gac gac gag acg ttc Ser Lys Pro Asn Asp Ile Glu Leu Phe Gln Ile Asp Asp Glu Thr Phe 305 310 315 | 1363 |

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| ttt gtc atc gca gac agc tca aag gct ggt ctg tcc aca gtt tat aaa Phe Val Ile Ala Asp Ser Ser Lys Ala Gly Leu Ser Thr Val Tyr Lys 320 325 330 | 1411 |
| tgg aac agc aaa gga ttc tat tct tac cag tca ctg cac gag tgg ttc Trp Asn Ser Lys Gly Phe Tyr Ser Tyr Gln Ser Leu His Glu Trp Phe 335 340 345 | 1459 |
| agg gac acg gat gcg gag ttt gtt gat atc gat gga aaa tcg cat ctc Arg Asp Thr Asp Ala Glu Phe Val Asp Ile Asp Gly Lys Ser His Leu 350 355 360 | 1507 |
| atc ctg tcc agc cgc tcc cag gtc ccc atc atc ctc cag tgg aat aaa Ile Leu Ser Ser Arg Ser Gln Val Pro Ile Ile Leu Gln Trp Asn Lys 365 370 375 380 | 1555 |
| agc tct aag aag ttt gtc ccc cat ggt gac atc ccc aac atg gag gac Ser Ser Lys Lys Phe Val Pro His Gly Asp Ile Pro Asn Met Glu Asp 385 390 395 | 1603 |
| gta ctg gct gtg aag agc ttc cga atg caa aat acc ctc tac ctt tcc Val Leu Ala Val Lys Ser Phe Arg Met Gln Asn Thr Leu Tyr Leu Ser 400 405 410 | 1651 |
| ctt acc cgc ttc atc ggg gac tcc cgg gtc atg agg tgg aac agt aag Leu Thr Arg Phe Ile Gly Asp Ser Arg Val Met Arg Trp Asn Ser Lys 415 420 425 | 1699 |
| cag ttt gtg gag atc caa gct ctt cca tcc cgg ggg gcc atg acc ctg Gln Phe Val Glu Ile Gln Ala Leu Pro Ser Arg Gly Ala Met Thr Leu 430 435 440 | 1747 |
| cag ccc ttt tct ttt aaa gat aat cac tac ctg gcc ctg ggg agt gac Gln Pro Phe Ser Phe Lys Asp Asn His Tyr Leu Ala Leu Gly Ser Asp 445 450 455 460 | 1795 |
| tat aca ttc tct cag ata tac cag tgg gat aaa gag aag cag cta ttc Tyr Thr Phe Ser Gln Ile Tyr Gln Trp Asp Lys Glu Lys Gln Leu Phe 465 470 475 | 1843 |
| aaa aag ttt aag gag att tac gtg cag gcg cct cgt tca ttc aca gct Lys Lys Phe Lys Glu Ile Tyr Val Gln Ala Pro Arg Ser Phe Thr Ala 480 485 490 | 1891 |
| gtc tcc acc gac agg aga gat ttc ttt ttt gca tcc agt ttc aaa ggg Val Ser Thr Asp Arg Arg Asp Phe Phe Ala Ser Ser Phe Lys Gly 495 500 505 | 1939 |
| aaa aca aag att ttt gaa cat ata att gtt gac tta agt ttg Lys Thr Lys Ile Phe Glu His Ile Ile Val Asp Leu Ser Leu 510 515 520 | 1981 |
| tgaagggtgtg gtgggtaaaa ctaagagaaa tgttagcatta gctctcacaa aagaggacca | 2041 |

agaaaaatca acaaacaaat caaagccagg ctcagagctc taaaattaaa aagcactgaa 2101
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atg 3664

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-5 -1 1 5

Leu Ala Arg Cys Pro Ala Thr Cys Ser Cys Thr Lys Glu Ser Ile Ile
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Cys Val Gly Ser Ser Trp Val Pro Arg Ile Val Pro Gly Asp Ile Ser
30 35 40

Ser Leu Ser Leu Val Asn Gly Thr Phe Ser Glu Ile Lys Asp Arg Met
45 50 55

Phe Ser His Leu Pro Ser Leu Gln Leu Leu Leu Asn Ser Asn Ser
60 65 70

Phe Thr Ile Ile Arg Asp Asp Ala Phe Ala Gly Leu Phe His Leu Glu
75 80 85

Tyr Leu Phe Ile Glu Gly Asn Lys Ile Glu Thr Ile Ser Arg Asn Ala
90 95 100 105

Phe Arg Gly Leu Arg Asp Leu Thr His Leu Ser Leu Ala Asn Asn His
110 115 120

Ile Lys Ala Leu Pro Arg Asp Val Phe Ser Asp Leu Asp Ser Leu Ile
125 130 135

Glu Leu Asp Leu Arg Gly Asn Lys Phe Glu Cys Asp Cys Lys Ala Lys
140 145 150

Trp Leu Tyr Leu Trp Leu Lys Met Thr Asn Ser Thr Val Ser Asp Val
155 160 165

Leu Cys Ile Gly Pro Pro Glu Tyr Gln Glu Lys Lys Leu Asn Asp Val
170 175 180 185

Thr Ser Phe Asp Tyr Glu Cys Thr Thr Asp Phe Val Val His Gln
190 195 200

Thr Leu Pro Tyr Gln Ser Val Ser Val Asp Thr Phe Asn Ser Lys Asn
205 210 215

Asp Val Tyr Val Ala Ile Ala Gln Pro Ser Met Glu Asn Cys Met Val
220 225 230

Leu Glu Trp Asp His Ile Glu Met Asn Phe Arg Ser Tyr Asp Asn Ile
235 240 245

Thr Gly Gln Ser Ile Val Gly Cys Lys Ala Ile Leu Ile Asp Asp Gln
250 255 260 265

Val Phe Val Val Ala Gln Leu Phe Gly Gly Ser His Ile Tyr Lys
270 275 280

Tyr Asp Glu Ser Trp Thr Lys Phe Val Lys Phe Gln Asp Ile Glu Val
285 290 295

Ser Arg Ile Ser Lys Pro Asn Asp Ile Glu Leu Phe Gln Ile Asp Asp
300 305 310

Glu Thr Phe Phe Val Ile Ala Asp Ser Ser Lys Ala Gly Leu Ser Thr
315 320 325

Val Tyr Lys Trp Asn Ser Lys Gly Phe Tyr Ser Tyr Gln Ser Leu His
330 335 340 345

Glu Trp Phe Arg Asp Thr Asp Ala Glu Phe Val Asp Ile Asp Gly Lys
350 355 360

Ser His Leu Ile Leu Ser Ser Arg Ser Gln Val Pro Ile Ile Leu Gln
365 370 375

Trp Asn Lys Ser Ser Lys Lys Phe Val Pro His Gly Asp Ile Pro Asn
380 385 390

Met Glu Asp Val Leu Ala Val Lys Ser Phe Arg Met Gln Asn Thr Leu
395 400 405

Tyr Leu Ser Leu Thr Arg Phe Ile Gly Asp Ser Arg Val Met Arg Trp
410 415 420 425

Asn Ser Lys Gln Phe Val Glu Ile Gln Ala Leu Pro Ser Arg Gly Ala
430 435 440

Met Thr Leu Gln Pro Phe Ser Phe Lys Asp Asn His Tyr Leu Ala Leu
445 450 455

Gly Ser Asp Tyr Thr Phe Ser Gln Ile Tyr Gln Trp Asp Lys Glu Lys
460 465 470

Gln Leu Phe Lys Lys Phe Lys Glu Ile Tyr Val Gln Ala Pro Arg Ser
475 480 485

Phe Thr Ala Val Ser Thr Asp Arg Arg Asp Phe Phe Ala Ser Ser
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Leu

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Ala Ala Leu Ala His Gly Cys Leu His Cys His Ser Asn Phe Ser Lys
-1 1 5 10

aag ttc tcc ttc tac cgc cac cat gtg aac ttc aag tcc tgg tgg gtg 147
Lys Phe Ser Phe Tyr Arg His His Val Asn Phe Lys Ser Trp Trp Val
15 20 25

ggc gac atc ccc gtg tca ggg gct ctg ctc acc gac tgg agc gac gac 195
Gly Asp Ile Pro Val Ser Gly Ala Leu Leu Thr Asp Trp Ser Asp Asp
30 35 40

acg atg aag gag ctg cac ctg gcc atc ccc gcc aag atc acc cgg gag 243
Thr Met Lys Glu Leu His Leu Ala Ile Pro Ala Lys Ile Thr Arg Glu
45 50 55 60

aag ctg gac caa gtg gct aca gca gtg tac cag atg atg gat cag ctg 291
Lys Leu Asp Gln Val Ala Thr Ala Val Tyr Gln Met Met Asp Gln Leu
65 70 75

tac cag ggg aag atg tac ttc ccc ggg tat ttc ccc aac gag ctg cga 339
Tyr Gln Gly Lys Met Tyr Phe Pro Gly Tyr Phe Pro Asn Glu Leu Arg
80 85 90

aac atc ttc cgg gag cag gtg cac ctc atc cag aac gcc atc atc gaa 387
Asn Ile Phe Arg Glu Gln Val His Leu Ile Gln Asn Ala Ile Ile Glu
95 100 105

agc cgc atc gac tgt cag cac cgc tgt ggc atc ttc cag tac gag acc 435
Ser Arg Ile Asp Cys Gln His Arg Cys Gly Ile Phe Gln Tyr Glu Thr
110 115 120

atc tcc tgc aac aac tgc aca gac tcg cac gtc gcc tgc ttt ggc tat 483
Ile Ser Cys Asn Asn Cys Thr Asp Ser His Val Ala Cys Phe Gly Tyr
125 130 135 140

aac tgc gag tcc tcg gct cag tgg aag tca gct gtc cag ggc ctc ctg 531
Asn Cys Glu Ser Ser Ala Gln Trp Lys Ser Ala Val Gln Gly Leu Leu
145 150 155

aac tac ata aat aac tgg cac aac ctg gta tcg cca gcc tta agg tgt 579
Asn Tyr Ile Asn Asn Trp His Asn Leu Val Ser Pro Ala Leu Arg Cys
160 165 170

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ctg gag ccc cca cac ttg gcc aac ctg acc ttg gaa aat gct gct gag 627
Leu Glu Pro Pro His Leu Ala Asn Leu Thr Leu Glu Asn Ala Ala Glu
175 180 185

tgt ctc aag cag cac tgacagcagc tgggcctgcc ccagggcaac gtggggcgg 682
Cys Leu Lys Gln His
190

agactcagct ggacagcccc tgcctgtcac tctggagctg ggctgctgct gcctcaggac 742
ccccctctccg acccccggaca gagctgagct ggccagggcc aggagggcgg gagggaggga 802
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attaaagtcc ctgatgttcc tcaaaaaaaaaaaaaaa 898

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5 10 15

Arg His His Val Asn Phe Lys Ser Trp Trp Val Gly Asp Ile Pro Val
20 25 30

Ser Gly Ala Leu Leu Thr Asp Trp Ser Asp Asp Thr Met Lys Glu Leu
35 40 45

His Leu Ala Ile Pro Ala Lys Ile Thr Arg Glu Lys Leu Asp Gln Val
50 55 60 65

Ala Thr Ala Val Tyr Gln Met Met Asp Gln Leu Tyr Gln Gly Lys Met
70 75 80

Tyr Phe Pro Gly Tyr Phe Pro Asn Glu Leu Arg Asn Ile Phe Arg Glu
85 90 95

Gln Val His Leu Ile Gln Asn Ala Ile Ile Glu Ser Arg Ile Asp Cys
100 105 110

Gln His Arg Cys Gly Ile Phe Gln Tyr Glu Thr Ile Ser Cys Asn Asn
 115 120 125

Cys Thr Asp Ser His Val Ala Cys Phe Gly Tyr Asn Cys Glu Ser Ser
 130 135 140 145

Ala Gln Trp Lys Ser Ala Val Gln Gly Leu Leu Asn Tyr Ile Asn Asn
 150 155 160

Trp His Asn Leu Val Ser Pro Ala Leu Arg Cys Leu Glu Pro Pro His
 165 170 175

Leu Ala Asn Leu Thr Leu Glu Asn Ala Ala Glu Cys Leu Lys Gln His
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atatTTgtt ccaaa atg gca tct tac ctt tat gga gta ctc ttt gct gtt 171

Met Ala Ser Tyr Leu Tyr Gly Val Leu Phe Ala Val
 -20 -15 -10

ggc ctc tgt gct cca atc tac tgt gtg tcc ccg gcc aat gcc ccc agt 219

Gly Leu Cys Ala Pro Ile Tyr Cys Val Ser Pro Ala Asn Ala Pro Ser
 -5 -1 1 5

gca tac ccc cgc cct tcc tcc aca aag agc acc cct gcc tca cag gtg 267

Ala Tyr Pro Arg Pro Ser Ser Thr Lys Ser Thr Pro Ala Ser Gln Val
 10 15 20

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| tat tcc ctc aac acc gac ttt gcc ttc cgc cta tac cgc agg ctg gtt | 315 |
| Tyr Ser Leu Asn Thr Asp Phe Ala Phe Arg Leu Tyr Arg Arg Leu Val | |
| 25 30 35 40 | |
| ttg gag acc ccg agt cag aac atc ttc ttc tcc cct gtg agt gtc tcc | 363 |
| Leu Glu Thr Pro Ser Gln Asn Ile Phe Phe Ser Pro Val Ser Val Ser | |
| 45 50 55 | |
| act tcc ctg gcc atg ctc tcc ctt ggg gcc cac tca gtc acc aag acc | 411 |
| Thr Ser Leu Ala Met Leu Ser Leu Gly Ala His Ser Val Thr Lys Thr | |
| 60 65 70 | |
| cag att ctc cag ggc ctg ggc ttc aac ctc aca cac aca cca gag tct | 459 |
| Gln Ile Leu Gln Gly Leu Gly Phe Asn Leu Thr His Thr Pro Glu Ser | |
| 75 80 85 | |
| gcc atc cac cag ggc ttc cag cac ctg gtt cac tca ctg act gtt ccc | 507 |
| Ala Ile His Gln Gly Phe Gln His Leu Val His Ser Leu Thr Val Pro | |
| 90 95 100 | |
| agc aaa gac ctg acc ttg aag atg gga agt gcc ctc ttc gtc aag aag | 555 |
| Ser Lys Asp Leu Thr Leu Lys Met Gly Ser Ala Leu Phe Val Lys Lys | |
| 105 110 115 120 | |
| gag ctg cag ctg cag gca aat ttc ttg ggc aat gtc aag agg ctg tat | 603 |
| Glu Leu Gln Leu Ala Asn Phe Leu Gly Asn Val Lys Arg Leu Tyr | |
| 125 130 135 | |
| gaa gca gaa gtc ttt tct aca gat ttc tcc aac ccc tcc att gcc cag | 651 |
| Glu Ala Glu Val Phe Ser Thr Asp Phe Ser Asn Pro Ser Ile Ala Gln | |
| 140 145 150 | |
| gcg agg atc aac agc cat gtg aaa aag aag acc caa ggg aag gtt gta | 699 |
| Ala Arg Ile Asn Ser His Val Lys Lys Thr Gln Gly Lys Val Val | |
| 155 160 165 | |
| gac ata atc caa ggc ctt gac ctt ctg acg gcc atg gtt ctg gtg aac | 747 |
| Asp Ile Ile Gln Gly Leu Asp Leu Leu Thr Ala Met Val Leu Val Asn | |
| 170 175 180 | |
| cac att ttc ttt aaa gcc aag tgg gag aag ccc ttt cac cct gaa tat | 795 |
| His Ile Phe Phe Lys Ala Lys Trp Glu Lys Pro Phe His Pro Glu Tyr | |
| 185 190 195 200 | |
| aca aga aag aac ttc cca ttc ctg gtg ggc gag cag gtc act gtg cat | 843 |
| Thr Arg Lys Asn Phe Pro Phe Leu Val Gly Glu Gln Val Thr Val His | |
| 205 210 215 | |
| gtc ccc atg atg cac cag aaa gag cag ttc gct ttt ggg gtg gat aca | 891 |
| Val Pro Met Met His Gln Lys Glu Gln Phe Ala Phe Gly Val Asp Thr | |
| 220 225 230 | |

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| gag ctg aac tgc ttt gtg ctg cag atg gat tac aag gga gat gcc gtg Glu Leu Asn Cys Phe Val Leu Gln Met Asp Tyr Lys Gly Asp Ala Val 235 240 245 | 939 |
| gcc ttc ttt gtc ctc cct agc aag ggc aag atg agg caa ctg gaa cag Ala Phe Phe Val Leu Pro Ser Lys Gly Lys Met Arg Gln Leu Glu Gln 250 255 260 | 987 |
| gcc ttg tca gcc aga aca ctg aga aag tgg agc cac tca ctc cag aaa Ala Leu Ser Ala Arg Thr Leu Arg Lys Trp Ser His Ser Leu Gln Lys 265 270 275 280 | 1035 |
| agg tgg ata gag gtg ttc atc ccc aga ttt tcc att tct gcc tcc tac Arg Trp Ile Glu Val Phe Ile Pro Arg Phe Ser Ile Ser Ala Ser Tyr 285 290 295 | 1083 |
| aat ctg gaa acc atc ctc ccg aag atg ggc atc caa aat gtc ttt gac Asn Leu Glu Thr Ile Leu Pro Lys Met Gly Ile Gln Asn Val Phe Asp 300 305 310 | 1131 |
| aaa aat gct gat ttt tct gga att gca aag aga gac tcc ctg cag gtt Lys Asn Ala Asp Phe Ser Gly Ile Ala Lys Arg Asp Ser Leu Gln Val 315 320 325 | 1179 |
| tct aaa gca acc cac aag gct gtg ctg gat gtc agt gaa gag ggc act Ser Lys Ala Thr His Lys Ala Val Leu Asp Val Ser Glu Glu Gly Thr 330 335 340 | 1227 |
| gag gcc aca gca gct acc acc acc aag ttc ata gtc cga tcg aag gat Glu Ala Thr Ala Ala Thr Thr Lys Phe Ile Val Arg Ser Lys Asp 345 350 355 360 | 1275 |
| ggc ccc tct tac ttc act gtc tcc ttc aat agg acc ttc ctg atg atg Gly Pro Ser Tyr Phe Thr Val Ser Phe Asn Arg Thr Phe Leu Met Met 365 370 375 | 1323 |
| att aca aat aaa gcc aca gac ggt att ctc ttt cta ggg aaa gtg gaa Ile Thr Asn Lys Ala Thr Asp Gly Ile Leu Phe Leu Gly Lys Val Glu 380 385 390 | 1371 |
| aat ccc act aaa tcc taggtggaa atggcctgtt aactgatggc acattgctaa Asn Pro Thr Lys Ser 395 | 1426 |
| tgccacaagaa ataacaacc acatccctct ttctgttctg agggcatt tgacccagg ggagctggat tcgctggcag ggatgccact tccaggctc aatcaccaaa ccatcaacag | 1486 1546 |
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-1 1 5 10

Pro Ser Ser Thr Lys Ser Thr Pro Ala Ser Gln Val Tyr Ser Leu Asn
15 20 25

Thr Asp Phe Ala Phe Arg Leu Tyr Arg Arg Leu Val Leu Glu Thr Pro
30 35 40

Ser Gln Asn Ile Phe Phe Ser Pro Val Ser Val Ser Thr Ser Leu Ala
45 50 55 60

Met Leu Ser Leu Gly Ala His Ser Val Thr Lys Thr Gln Ile Leu Gln
65 70 75

Gly Leu Gly Phe Asn Leu Thr His Thr Pro Glu Ser Ala Ile His Gln
80 85 90

Gly Phe Gln His Leu Val His Ser Leu Thr Val Pro Ser Lys Asp Leu
95 100 105

Thr Leu Lys Met Gly Ser Ala Leu Phe Val Lys Lys Glu Leu Gln Leu
110 115 120

Gln Ala Asn Phe Leu Gly Asn Val Lys Arg Leu Tyr Glu Ala Glu Val
125 130 135 140

Phe Ser Thr Asp Phe Ser Asn Pro Ser Ile Ala Gln Ala Arg Ile Asn
145 150 155

Ser His Val Lys Lys Lys Thr Gln Gly Lys Val Val Asp Ile Ile Gln
160 165 170

Gly Leu Asp Leu Leu Thr Ala Met Val Leu Val Asn His Ile Phe Phe
175 180 185

Lys Ala Lys Trp Glu Lys Pro Phe His Pro Glu Tyr Thr Arg Lys Asn
190 195 200

Phe Pro Phe Leu Val Gly Glu Gln Val Thr Val His Val Pro Met Met
205 210 215 220

His Gln Lys Glu Gln Phe Ala Phe Gly Val Asp Thr Glu Leu Asn Cys
225 230 235

Phe Val Leu Gln Met Asp Tyr Lys Gly Asp Ala Val Ala Phe Phe Val
240 245 250

Leu Pro Ser Lys Gly Lys Met Arg Gln Leu Glu Gln Ala Leu Ser Ala
255 260 265

Arg Thr Leu Arg Lys Trp Ser His Ser Leu Gln Lys Arg Trp Ile Glu
270 275 280

Val Phe Ile Pro Arg Phe Ser Ile Ser Ala Ser Tyr Asn Leu Glu Thr
285 290 295 300

Ile Leu Pro Lys Met Gly Ile Gln Asn Val Phe Asp Lys Asn Ala Asp
305 310 315

Phe Ser Gly Ile Ala Lys Arg Asp Ser Leu Gln Val Ser Lys Ala Thr
320 325 330

His Lys Ala Val Leu Asp Val Ser Glu Glu Gly Thr Glu Ala Thr Ala
335 340 345

Ala Thr Thr Thr Lys Phe Ile Val Arg Ser Lys Asp Gly Pro Ser Tyr
350 355 360

Phe Thr Val Ser Phe Asn Arg Thr Phe Leu Met Met Ile Thr Asn Lys
365 370 375 380

Ala Thr Asp Gly Ile Leu Phe Leu Gly Lys Val Glu Asn Pro Thr Lys
 385 390 395

Ser

<210> 11
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<220>
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<222> (12)..(1682)

<220>
<221> mat_peptide
<222> (96)..()

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<220>
<221> variation
<222> (82)..(82)
<223> wherein n is A, G, C, or T
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<400> 11
tcaccaccat c atg gtg tcc acc gcc atg ggc tgc atc acc ttc ctg ggc
Met Val Ser Thr Ala Met Gly Cys Ile Thr Phe Leu Gly
-25 -20

50

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gtg gtc ctc ttg ctg ctt tcg tgc tgc tgt tnc gtg tgg agc cgc aac
Val Val Leu Leu Leu Leu Ser Cys Cys Cys Xaa Val Trp Ser Arg Asn
-15           -10           -5           -1   1

```

98

```

cgc atc cgc tgc ctg aac ccg ggc gac ctg gcc gcg ctg ccc gcg ctg
Arg Ile Arg Cys Leu Asn Pro Gly Asp Leu Ala Ala Leu Pro Ala Leu
      5           10          15

```

146

gag gag ctg gac ctg agc gag aac gcc atc gcg cac gtg gag ccc ggc
Glu Glu Leu Asp Leu Ser Glu Asn Ala Ile Ala His Val Glu Pro Gly
20 25 30

194

| | | |
|---|----|----|
| gcc ttc gcc aac ctg ccg cgc ctg cgc gtc ctg cgt ctc cgt ggc aac | | |
| Ala Phe Ala Asn Leu Pro Arg Leu Arg Val Leu Arg Leu Arg Gly Asn | | |
| 35 | 40 | 45 |

242

cag ctg aag ctc atc ccg ccc ggg gtc ttc acg cgc ctg gac aac ctc
 Gln Leu Lys Leu Ile Pro Pro Gly Val Phe Thr Arg Leu Asp Asn Leu
 50 55 60 65

| | |
|---|-----|
| acg ctg ctg gac ctg agc gag aac aag ctg gta atc ctg ctg gac tac | 338 |
| Thr Leu Leu Asp Leu Ser Glu Asn Lys Leu Val Ile Leu Leu Asp Tyr | |
| 70 75 80 | |
| act ttc cag gac ctg cac agc ctg cgc cg ^g ctg gaa gtg ggc gac aac | 386 |
| Thr Phe Gln Asp Leu His Ser Leu Arg Arg Leu Glu Val Gly Asp Asn | |
| 85 90 95 | |
| gac ctg gta ttc gtc tcg cgc cgc gcc ttc g ^c ggg ctg ctg gcc ctg | 434 |
| Asp Leu Val Phe Val Ser Arg Arg Ala Phe Ala Gly Leu Leu Ala Leu | |
| 100 105 110 | |
| gag gag ctg acc ctg gag cgc tgc aac ctc acg gct ctg tcc ggg gag | 482 |
| Glu Glu Leu Thr Leu Glu Arg Cys Asn Leu Thr Ala Leu Ser Gly Glu | |
| 115 120 125 | |
| tcg ctg ggc cat ctg cgc agc ctg ggc gcc ctg cgg ctg cgc cac ctg | 530 |
| Ser Leu Gly His Leu Arg Ser Leu Gly Ala Leu Arg Leu Arg His Leu | |
| 130 135 140 145 | |
| gcc atc gcc tcc ctg gag gac cag aac ttc cgc agg ctg ccc ggg ctg | 578 |
| Ala Ile Ala Ser Leu Glu Asp Gln Asn Phe Arg Arg Leu Pro Gly Leu | |
| 150 155 160 | |
| ctg cac ctg gag att gac aac tgg ccg ctg ctg gag gag gtg gcg g ^c g ^c | 626 |
| Leu His Leu Glu Ile Asp Asn Trp Pro Leu Leu Glu Val Ala Ala | |
| 165 170 175 | |
| ggc agc ctg cgg ggc ctg aac ctg acc tcg ctg tcg gtc acc cac acc | 674 |
| Gly Ser Leu Arg Gly Leu Asn Leu Thr Ser Leu Ser Val Thr His Thr | |
| 180 185 190 | |
| aac atc acc gcc gtg ccg gcc g ^c ctg cgg cac cag g ^c cac ctc | 722 |
| Asn Ile Thr Ala Val Pro Ala Ala Leu Arg His Gln Ala His Leu | |
| 195 200 205 | |
| acc tgc ctc aat ctg tcg cac aac ccc atc acg acg gtg ccg cgg ggg | 770 |
| Thr Cys Leu Asn Leu Ser His Asn Pro Ile Ser Thr Val Pro Arg Gly | |
| 210 215 220 225 | |
| tcg ttc cgg gac ctg gtc cgc ctg cgc gag ctg cac ctg gcc ggg g ^c | 818 |
| Ser Phe Arg Asp Leu Val Arg Leu Arg Glu Leu His Leu Ala Gly Ala | |
| 230 235 240 | |
| ctg ctg gct gtg gtg gag ccg cag gcc ttc ctg ggc ctg cgc cag atc | 866 |
| Leu Leu Ala Val Val Glu Pro Gln Ala Phe Leu Gly Leu Arg Gln Ile | |
| 245 250 255 | |
| cgc ctg ctc aac ctc tcc aac aac ctg ctc tcc acg ttg gag gag agc | 914 |
| Arg Leu Leu Asn Leu Ser Asn Asn Leu Leu Ser Thr Leu Glu Glu Ser | |
| 260 265 270 | |

| | |
|---|------|
| acc ttc cac tcg gtg aac acg cta gag acg ctg cgc gtg gac ggg aac Thr Phe His Ser Val Asn Thr Leu Glu Thr Leu Arg Val Asp Gly Asn 275 280 285 | 962 |
| ccg ctg gcc tgc gac tgt cgc ctg tgg atc gtg cag cgt cgc aag Pro Leu Ala Cys Asp Cys Arg Leu Leu Trp Ile Val Gln Arg Arg Lys 290 295 300 305 | 1010 |
| acc ctc aac ttc gac ggg cgg ctg ccg gcc tgc acc ccg gcc gag Thr Leu Asn Phe Asp Gly Arg Leu Pro Ala Cys Ala Thr Pro Ala Glu 310 315 320 | 1058 |
| gtg cgc ggc gac gcg ctg cga aac ctg ccg gac tcc gtg ctg ttc gag Val Arg Gly Asp Ala Leu Arg Asn Leu Pro Asp Ser Val Leu Phe Glu 325 330 335 | 1106 |
| tac ttc gtg tgc cgc aaa ccc aag atc cgg gag cgg cgg ctg cag cgc Tyr Phe Val Cys Arg Lys Pro Lys Ile Arg Glu Arg Arg Leu Gln Arg 340 345 350 | 1154 |
| gtc acg gcc acc gcg ggc gaa gac gtc cgc ttc ctc tgc cgc gcc gag Val Thr Ala Thr Ala Gly Glu Asp Val Arg Phe Leu Cys Arg Ala Glu 355 360 365 | 1202 |
| ggc gag ccg cgc ccc acc gtg gcc tgg gtg acc ccc cag cac ccc cgg ccc Gly Glu Pro Ala Pro Thr Val Ala Trp Val Thr Pro Gln His Arg Pro 370 375 380 385 | 1250 |
| gtg acg gcc acc agc gcg ggc cgg cgc gtg ctc ccc ggg ggg acg Val Thr Ala Thr Ser Ala Gly Arg Ala Arg Val Leu Pro Gly Gly Thr 390 395 400 | 1298 |
| ctg gag atc cag gac gcg cgg ccg cag gac agc ggc acc tac acg tgc Leu Glu Ile Gln Asp Ala Arg Pro Gln Asp Ser Gly Thr Tyr Thr Cys 405 410 415 | 1346 |
| gtg gcc agc aac gcg ggc aac gac acc tac ttc gcc acg ctg acc Val Ala Ser Asn Ala Gly Gly Asn Asp Thr Tyr Phe Ala Thr Leu Thr 420 425 430 | 1394 |
| gtg cgc ccc gag ccg gcc aac cgg acc ccg ggc gag gcc cac aac Val Arg Pro Glu Pro Ala Ala Asn Arg Thr Pro Gly Glu Ala His Asn 435 440 445 | 1442 |
| gag acg ctg gcg gcc ctg cgc cgg ctc gac ctc acc acc atc ctg Glu Thr Leu Ala Ala Leu Arg Ala Pro Leu Asp Leu Thr Thr Ile Leu 450 455 460 465 | 1490 |
| gtg tcc acc gcc atg ggc tgc atc acc ttc ctg ggc gtg gtc ctc ttc Val Ser Thr Ala Met Gly Cys Ile Thr Phe Leu Gly Val Val Leu Phe 470 475 480 | 1538 |

| | |
|--|------|
| tgc ttc gtg ctg ctg ttc gtg tgg agc cgc ggc cgc ggg cag cac aaa | 1586 |
| Cys Phe Val Leu Leu Phe Val Trp Ser Arg Gly Arg Gly Gln His Lys | |
| 485 | 490 |
| 495 | |
| aac aac ttc tcg gtg gag tac tcc ttc cgc aag gtg gat ggg ccg gcc | 1634 |
| Asn Asn Phe Ser Val Glu Tyr Ser Phe Arg Lys Val Asp Gly Pro Ala | |
| 500 | 505 |
| 510 | |
| gcc gcg gcg ggc cag gga ggc gcg cgc aag ttc aac atg aag atg atc | 1682 |
| Ala Ala Ala Gly Gln Gly Ala Arg Lys Phe Asn Met Lys Met Ile | |
| 515 | 520 |
| 525 | |
| tgaggggtcc ccagggcgga ccctccctc ccctcccccg cggggccggcc gctcgctgt | 1742 |
| ccacctatgc atttcccgga ggggaagggg acggctgcac ggcgctcccc aggcagaact | 1802 |
| tccccctttt ttgttagacgc ccaaccgcag gactgtttt catcagcatg cgtcttttt | 1862 |
| gcagtttctc aagcgtttc taaagatttc aaccgcgtt cctgtccctg ctatggtggc | 1922 |
| tgagctgggg ggtgggggtg cgggctgcaa ggtatgggggg atgggctccc gtctaccaac | 1982 |
| ccgggggtggc tgggggcgct cagagacccc aggatcctca gggcccgcaa ttcacaccca | 2042 |
| ggaggcacaa gactgctgcc cccaaaggccct gggcttcc | 2080 |

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<400> 12

Met Val Ser Thr Ala Met Gly Cys Ile Thr Phe Leu Gly Val Val Leu
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Leu Leu Leu Ser Cys Cys Cys Xaa Val Trp Ser Arg Asn Arg Ile Arg
 -10 -5 -1 1

Cys Leu Asn Pro Gly Asp Leu Ala Ala Leu Pro Ala Leu Glu Glu Leu
 5 10 15 20

Asp Leu Ser Glu Asn Ala Ile Ala His Val Glu Pro Gly Ala Phe Ala
 25 30 35

Asn Leu Pro Arg Leu Arg Val Leu Arg Leu Arg Gly Asn Gln Leu Lys
 40 45 50

Leu Ile Pro Pro Gly Val Phe Thr Arg Leu Asp Asn Leu Thr Leu Leu
55 60 65

Asp Leu Ser Glu Asn Lys Leu Val Ile Leu Leu Asp Tyr Thr Phe Gln
70 75 80

Asp Leu His Ser Leu Arg Arg Leu Glu Val Gly Asp Asn Asp Leu Val
85 90 95 100

Phe Val Ser Arg Arg Ala Phe Ala Gly Leu Leu Ala Leu Glu Glu Leu
105 110 115

Thr Leu Glu Arg Cys Asn Leu Thr Ala Leu Ser Gly Glu Ser Leu Gly
120 125 130

His Leu Arg Ser Leu Gly Ala Leu Arg Leu Arg His Leu Ala Ile Ala
135 140 145

Ser Leu Glu Asp Gln Asn Phe Arg Arg Leu Pro Gly Leu Leu His Leu
150 155 160

Glu Ile Asp Asn Trp Pro Leu Leu Glu Glu Val Ala Ala Gly Ser Leu
165 170 175 180

Arg Gly Leu Asn Leu Thr Ser Leu Ser Val Thr His Thr Asn Ile Thr
185 190 195

Ala Val Pro Ala Ala Ala Leu Arg His Gln Ala His Leu Thr Cys Leu
200 205 210

Asn Leu Ser His Asn Pro Ile Ser Thr Val Pro Arg Gly Ser Phe Arg
215 220 225

Asp Leu Val Arg Leu Arg Glu Leu His Leu Ala Gly Ala Leu Leu Ala
230 235 240

Val Val Glu Pro Gln Ala Phe Leu Gly Leu Arg Gln Ile Arg Leu Leu
245 250 255 260

Asn Leu Ser Asn Asn Leu Leu Ser Thr Leu Glu Glu Ser Thr Phe His
265 270 275

Ser Val Asn Thr Leu Glu Thr Leu Arg Val Asp Gly Asn Pro Leu Ala
280 285 290

Cys Asp Cys Arg Leu Leu Trp Ile Val Gln Arg Arg Lys Thr Leu Asn
295 300 305

Phe Asp Gly Arg Leu Pro Ala Cys Ala Thr Pro Ala Glu Val Arg Gly
310 315 320

Asp Ala Leu Arg Asn Leu Pro Asp Ser Val Leu Phe Glu Tyr Phe Val
325 330 335 340

Cys Arg Lys Pro Lys Ile Arg Glu Arg Arg Leu Gln Arg Val Thr Ala
345 350 355

Thr Ala Gly Glu Asp Val Arg Phe Leu Cys Arg Ala Glu Gly Glu Pro
360 365 370

Ala Pro Thr Val Ala Trp Val Thr Pro Gln His Arg Pro Val Thr Ala
375 380 385

Thr Ser Ala Gly Arg Ala Arg Val Leu Pro Gly Gly Thr Leu Glu Ile
390 395 400

Gln Asp Ala Arg Pro Gln Asp Ser Gly Thr Tyr Thr Cys Val Ala Ser
405 410 415 420

Asn Ala Gly Gly Asn Asp Thr Tyr Phe Ala Thr Leu Thr Val Arg Pro
425 430 435

Glu Pro Ala Ala Asn Arg Thr Pro Gly Glu Ala His Asn Glu Thr Leu
440 445 450

Ala Ala Leu Arg Ala Pro Leu Asp Leu Thr Thr Ile Leu Val Ser Thr
455 460 465

Ala Met Gly Cys Ile Thr Phe Leu Gly Val Val Leu Phe Cys Phe Val
470 475 480

Leu Leu Phe Val Trp Ser Arg Gly Arg Gly Gln His Lys Asn Asn Phe
 485 490 495 500

Ser Val Glu Tyr Ser Phe Arg Lys Val Asp Gly Pro Ala Ala Ala
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Gly Gln Gly Gly Ala Arg Lys Phe Asn Met Lys Met Ile
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 Met Thr Cys

57

tgg ctg tgc gtc ctg agc ctg ccc ctg ctc ctg ctg ccc gcg gcg ccg
 Trp Leu Cys Val Leu Ser Leu Pro Leu Leu Leu Pro Ala Ala Pro
 -20 -15 -10

105

ccc ccg gct gga ggc tgc ccg gcc ccg tgc gag tgc acc gtg cag acc
 Pro Pro Ala Gly Gly Cys Pro Ala Arg Cys Glu Cys Thr Val Gln Thr
 -5 -1 1 5 10

153

cgc gcg gtg gcc tgc acg ccg ccg ctg acc gcc gtg ccc gac ggc
 Arg Ala Val Ala Cys Thr Arg Arg Arg Leu Thr Ala Val Pro Asp Gly
 15 20 25

201

atc ccg gcc gag acc ccg ctg ctg gag ctc agc ccg aac ccg atc ccg
 Ile Pro Ala Glu Thr Arg Leu Leu Glu Leu Ser Arg Asn Arg Ile Arg
 30 35 40

249

tgc ctg aac ccg ggc gac ctg gcc ccg ctg ccc gcg ctg gag gag ctg
 Cys Leu Asn Pro Gly Asp Leu Ala Ala Leu Pro Ala Leu Glu Leu
 45 50 55

297

gac ctg agc gag aac gcc atc ccg cac gtg gag ccc ggc gcc ttc gcc
 Asp Leu Ser Glu Asn Ala Ile Ala His Val Glu Pro Gly Ala Phe Ala
 60 65 70 75

345

| | | | |
|---|-----|-----|-----|
| aac ctg ccg cgc ctg cgc gtc ctg cgt ctc cgt ggc aac cag ctg aag | 393 | | |
| Asn Leu Pro Arg Leu Arg Val Leu Arg Leu Arg Gly Asn Gln Leu Lys | | | |
| 80 | 85 | 90 | |
| ctc atc ccg ccc ggg gtc ttc acg cgc ctg gac aac ctc acg ctg ctg | 441 | | |
| Leu Ile Pro Pro Gly Val Phe Thr Arg Leu Asp Asn Leu Thr Leu Leu | | | |
| 95 | 100 | 105 | |
| gac ctg agc gag aac aag ctg gta atc ctg ctg gac tac act ttc cag | 489 | | |
| Asp Leu Ser Glu Asn Lys Leu Val Ile Leu Leu Asp Tyr Thr Phe Gln | | | |
| 110 | 115 | 120 | |
| gac ctg cac agc ctg cgc cgg ctg gaa gtg ggc gac aac gac ctg gta | 537 | | |
| Asp Leu His Ser Leu Arg Arg Leu Glu Val Gly Asp Asn Asp Leu Val | | | |
| 125 | 130 | 135 | |
| ttc gtc tcg cgc cgc gcc ttc gcg ggg ctg ctg gcc ctg gag gag ctg | 585 | | |
| Phe Val Ser Arg Arg Ala Phe Ala Gly Leu Leu Ala Leu Glu Glu Leu | | | |
| 140 | 145 | 150 | 155 |
| acc ctg gag cgc tgc aac ctc acg gct ctg tcc ggg gag tcg ctg ggc | 633 | | |
| Thr Leu Glu Arg Cys Asn Leu Thr Ala Leu Ser Gly Glu Ser Leu Gly | | | |
| 160 | 165 | 170 | |
| cat ctg cgc agc ctg ggc gcc ctg cgg ctg cgc cac ctg gcc atc gcc | 681 | | |
| His Leu Arg Ser Leu Gly Ala Leu Arg Leu Arg His Leu Ala Ile Ala | | | |
| 175 | 180 | 185 | |
| tcc ctg gag gac cag aac ttc cgc agg ctg ccc ggg ctg ctg cac ctg | 729 | | |
| Ser Leu Glu Asp Gln Asn Phe Arg Arg Leu Pro Gly Leu Leu His Leu | | | |
| 190 | 195 | 200 | |
| gag att gac aac tgg ccg ctg ctg gag gag gtg gcg gcg ggc agc ctg | 777 | | |
| Glu Ile Asp Asn Trp Pro Leu Leu Glu Val Ala Ala Gly Ser Leu | | | |
| 205 | 210 | 215 | |
| cgg ggc ctg aac ctg acc tcg ctg tcg gtc acc cac acc aac atc acc | 825 | | |
| Arg Gly Leu Asn Leu Thr Ser Leu Ser Val Thr His Thr Asn Ile Thr | | | |
| 220 | 225 | 230 | 235 |
| gcc gtg ccg gcc ggc ctg cgg cac cag gcg cac ctc acc tgc ctc | 873 | | |
| Ala Val Pro Ala Ala Leu Arg His Gln Ala His Leu Thr Cys Leu | | | |
| 240 | 245 | 250 | |
| aat ctg tcg cac aac ccc atc agc acg gtg ccg cgg ggg tcg ttc cgg | 921 | | |
| Asn Leu Ser His Asn Pro Ile Ser Thr Val Pro Arg Gly Ser Phe Arg | | | |
| 255 | 260 | 265 | |
| gac ctg gtc cgc ctg cgc gag ctg cac ctg gcc ggg gcc ctg ctg gct | 969 | | |
| Asp Leu Val Arg Leu Arg Glu Leu His Leu Ala Gly Ala Leu Leu Ala | | | |
| 270 | 275 | 280 | |

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|
| gtg | gtg | gag | ccg | cag | gcc | ttc | ctg | ggc | ctg | cgc | cag | atc | cgc | ctg | ctc | 1017 |
| Val | Val | Glu | Pro | Gln | Ala | Phe | Leu | Gly | Leu | Arg | Gln | Ile | Arg | Leu | Leu | |
| 285 | | | | | | | 290 | | | | | 295 | | | | |
| aac | ctc | tcc | aac | aac | ctg | ctc | acg | ttg | gag | gag | agc | acc | ttc | cac | 1065 | |
| Asn | Leu | Ser | Asn | Asn | Leu | Leu | Ser | Thr | Leu | Glu | Glu | Ser | Thr | Phe | His | |
| 300 | | | | | | | 305 | | | | 310 | | 315 | | | |
| tcg | gtg | aac | acg | cta | gag | acg | ctg | cgc | gtg | gac | ggg | aac | ccg | ctg | gcc | 1113 |
| Ser | Val | Asn | Thr | Leu | Glu | Thr | Leu | Arg | Val | Asp | Gly | Asn | Pro | Leu | Ala | |
| 320 | | | | | | | 325 | | | | 330 | | | | | |
| tgc | gac | tgt | cgc | ctg | ctg | tgg | atc | gtg | cag | cgt | cgc | aag | acc | ctc | aac | 1161 |
| Cys | Asp | Cys | Arg | Leu | Leu | Trp | Ile | Val | Gln | Arg | Arg | Lys | Thr | Leu | Asn | |
| 335 | | | | | | | 340 | | | | 345 | | | | | |
| ttc | gac | ggg | cg | ctg | ccg | gcc | tgc | gcc | acc | ccg | gcc | gag | gtg | cgc | ggc | 1209 |
| Phe | Asp | Gly | Arg | Leu | Pro | Ala | Cys | Ala | Thr | Pro | Ala | Glu | Val | Arg | Gly | |
| 350 | | | | | | | 355 | | | | 360 | | | | | |
| gac | g | ctg | cg | a | ac | ctg | ccg | gac | tcc | gtg | ctg | ttc | gag | tac | ttc | 1257 |
| Asp | A | Leu | G | A | S | Leu | P | A | S | S | Leu | Phe | Glu | Tyr | Phe | Val |
| 365 | | | | | | | 370 | | | | 375 | | | | | |
| tgc | cgc | aaa | ccc | aag | atc | cg | g | cg | cg | ctg | cag | cgc | gtc | acg | gcc | 1305 |
| Cys | Arg | Lys | Pro | Lys | Ile | Arg | Glu | Arg | Arg | Leu | Gln | Arg | Val | Thr | Ala | |
| 380 | | | | | | | 385 | | | | 390 | | 395 | | | |
| acc | g | cg | g | aa | g | a | g | c | tc | tgc | ccg | g | ccg | g | ccg | 1353 |
| Thr | A | l | G | Y | G | A | G | l | tc | tgc | ccg | g | ccg | g | ccg | |
| 400 | | | | | | | 405 | | | | 410 | | | | | |
| gcg | ccc | acc | gt | g | cc | tgg | gt | acc | ccc | cag | cac | cg | ccg | gt | acg | 1401 |
| Ala | Pro | Thr | Val | Ala | Trp | Val | Thr | Pro | Gln | His | Arg | Pro | Val | Thr | Ala | |
| 415 | | | | | | | 420 | | | | 425 | | | | | |
| acc | agc | g | cg | g | cg | g | cg | gt | ctc | ccc | gg | gg | ac | ctg | g | 1449 |
| Thr | Ser | A | G | Y | A | G | Y | G | tc | ccc | gg | gg | ac | ctg | g | |
| 430 | | | | | | | 435 | | | | 440 | | | | | |
| cag | g | ac | g | cg | cc | cag | g | ac | tc | ac | cg | tgc | gt | cc | agc | 1497 |
| Gln | Asp | Ala | Arg | Pro | Gln | Asp | Ser | Gly | Thr | Tyr | Thr | Cys | Val | Ala | Ser | |
| 445 | | | | | | | 450 | | | | 455 | | | | | |
| aac | g | cg | g | cc | a | ac | g | ac | ttc | gg | ac | gt | cc | cc | 1545 | |
| Asn | Ala | Gly | Gly | Asn | Asp | Thr | Tyr | Phe | Ala | Thr | Leu | Thr | Val | Arg | Pro | |
| 460 | | | | | | | 465 | | | | 470 | | 475 | | | |
| gag | cc | gc | gc | a | ac | cc | cg | gg | g | cc | cac | a | ac | g | ct | 1593 |
| Glu | Pro | Ala | Ala | Asn | Arg | Thr | Pro | Gly | Ala | His | Asn | Glu | Thr | Leu | | |
| 480 | | | | | | | 485 | | | | 490 | | | | | |

| | |
|--|------|
| gcg gcc ctg cgc gcg ccg ctc gac ctc acc acc atc ctg gtg tcc acc | 1641 |
| Ala Ala Leu Arg Ala Pro Leu Asp Leu Thr Thr Ile Leu Val Ser Thr | |
| 495 500 505 | |
| gcc atg ggc tgc atc acc ttc ctg ggc gtg gtc ctc ttc tgc ttc gtg | 1689 |
| Ala Met Gly Cys Ile Thr Phe Leu Gly Val Val Leu Phe Cys Phe Val | |
| 510 515 520 | |
| ctg ctg ttc gtg tgg agc cgc ggc cgc ggg cag cac aaa aac aac ttc | 1737 |
| Leu Leu Phe Val Trp Ser Arg Gly Arg Gly Gln His Lys Asn Asn Phe | |
| 525 530 535 | |
| tcg gtg gag tac tcc ttc cgc aag gtg gat ggg ccg gcc gcc gcg | 1785 |
| Ser Val Glu Tyr Ser Phe Arg Lys Val Asp Gly Pro Ala Ala Ala | |
| 540 545 550 555 | |
| ggc cag gga ggc gcg cgc aag ttc aac atg aag atg atc tgaggggtcc | 1834 |
| Gly Gln Gly Ala Arg Lys Phe Asn Met Lys Met Ile | |
| 560 565 | |
| ccagggcgga ccctccccctc ccctcccccg cgggccccggcc gctcgctgt ccacctatgc | 1894 |
| atttccccggaa gggaaaggggg acggctgcac ggcgcctccc aggcagaact tccccctttt | 1954 |
| ttgttagacgc ccaaccgcag gactgttttt catcagcatg cgtcttttt gcagtttctc | 2014 |
| aagcgttttc taaagatttc aaccctgtttt cctgtccctg ctatggtggc tgagctgggg | 2074 |
| ggtgggggtg cgggctgcaa ggtggggggg atgggctccc gtctaccaac cgggggtggc | 2134 |
| tggggcgct cagagacccc aggatcctca gggcccgcaa ttcacacccca ggaggcacaa | 2194 |
| gactgctgcc cccaaaggccct gggcttcc | 2222 |

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<400> 14

Met Thr Cys Trp Leu Cys Val Leu Ser Leu Pro Leu Leu Leu Pro
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Ala Ala Pro Pro Pro Ala Gly Gly Cys Pro Ala Arg Cys Glu Cys Thr
 -5 -1 1 5

Val Gln Thr Arg Ala Val Ala Cys Thr Arg Arg Arg Leu Thr Ala Val
 10 15 20

Pro Asp Gly Ile Pro Ala Glu Thr Arg Leu Leu Glu Leu Ser Arg Asn
25 30 35 40

Arg Ile Arg Cys Leu Asn Pro Gly Asp Leu Ala Ala Leu Pro Ala Leu
45 50 55

Glu Glu Leu Asp Leu Ser Glu Asn Ala Ile Ala His Val Glu Pro Gly
60 65 70

Ala Phe Ala Asn Leu Pro Arg Leu Arg Val Leu Arg Leu Arg Gly Asn
75 80 85

Gln Leu Lys Leu Ile Pro Pro Gly Val Phe Thr Arg Leu Asp Asn Leu
90 95 100

Thr Leu Leu Asp Leu Ser Glu Asn Lys Leu Val Ile Leu Leu Asp Tyr
105 110 115 120

Thr Phe Gln Asp Leu His Ser Leu Arg Arg Leu Glu Val Gly Asp Asn
125 130 135

Asp Leu Val Phe Val Ser Arg Arg Ala Phe Ala Gly Leu Leu Ala Leu
140 145 150

Glu Glu Leu Thr Leu Glu Arg Cys Asn Leu Thr Ala Leu Ser Gly Glu
155 160 165

Ser Leu Gly His Leu Arg Ser Leu Gly Ala Leu Arg Leu Arg His Leu
170 175 180

Ala Ile Ala Ser Leu Glu Asp Gln Asn Phe Arg Arg Leu Pro Gly Leu
185 190 195 200

Leu His Leu Glu Ile Asp Asn Trp Pro Leu Leu Glu Val Ala Ala
205 210 215

Gly Ser Leu Arg Gly Leu Asn Leu Thr Ser Leu Ser Val Thr His Thr
220 225 230

Asn Ile Thr Ala Val Pro Ala Ala Leu Arg His Gln Ala His Leu
235 240 245

Thr Cys Leu Asn Leu Ser His Asn Pro Ile Ser Thr Val Pro Arg Gly
250 255 260

Ser Phe Arg Asp Leu Val Arg Leu Arg Glu Leu His Leu Ala Gly Ala
265 270 275 280

Leu Leu Ala Val Val Glu Pro Gln Ala Phe Leu Gly Leu Arg Gln Ile
285 290 295

Arg Leu Leu Asn Leu Ser Asn Asn Leu Leu Ser Thr Leu Glu Glu Ser
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Thr Phe His Ser Val Asn Thr Leu Glu Thr Leu Arg Val Asp Gly Asn
315 320 325

Pro Leu Ala Cys Asp Cys Arg Leu Leu Trp Ile Val Gln Arg Arg Lys
330 335 340

Thr Leu Asn Phe Asp Gly Arg Leu Pro Ala Cys Ala Thr Pro Ala Glu
345 350 355 360

Val Arg Gly Asp Ala Leu Arg Asn Leu Pro Asp Ser Val Leu Phe Glu
365 370 375

Tyr Phe Val Cys Arg Lys Pro Lys Ile Arg Glu Arg Arg Leu Gln Arg
380 385 390

Val Thr Ala Thr Ala Gly Glu Asp Val Arg Phe Leu Cys Arg Ala Glu
395 400 405

Gly Glu Pro Ala Pro Thr Val Ala Trp Val Thr Pro Gln His Arg Pro
410 415 420

Val Thr Ala Thr Ser Ala Gly Arg Ala Arg Val Leu Pro Gly Gly Thr
425 430 435 440

Leu Glu Ile Gln Asp Ala Arg Pro Gln Asp Ser Gly Thr Tyr Thr Cys
445 450 455

Val Ala Ser Asn Ala Gly Gly Asn Asp Thr Tyr Phe Ala Thr Leu Thr
 460 465 470

Val Arg Pro Glu Pro Ala Ala Asn Arg Thr Pro Gly Glu Ala His Asn
 475 480 485

Glu Thr Leu Ala Ala Leu Arg Ala Pro Leu Asp Leu Thr Thr Ile Leu
 490 495 500

Val Ser Thr Ala Met Gly Cys Ile Thr Phe Leu Gly Val Val Leu Phe
 505 510 515 520

Cys Phe Val Leu Leu Phe Val Trp Ser Arg Gly Arg Gly Gln His Lys
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 Cys Leu Asn Gly Ser Gln Leu Ala Val Ala Ala Gly Gly Ser Gly Arg
 -10 -5 -1 1 5

gcg cgg ggc gcc gac acc tgt ggc tgg agg gga gtg ggg cca gcc agc 144
 Ala Arg Gly Ala Asp Thr Cys Gly Trp Arg Gly Val Gly Pro Ala Ser
 10 15 20

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| aga aac agt ggg ctg tac aac atc acc ttc aaa tat gac aat tgt acc | 192 |
| Arg Asn Ser Gly Leu Tyr Asn Ile Thr Phe Lys Tyr Asp Asn Cys Thr | |
| 25 30 35 | |
| acc tac ttg aat cca gtg ggg aag cat gtg att gct gac gcc cag aat | 240 |
| Thr Tyr Leu Asn Pro Val Gly Lys His Val Ile Ala Asp Ala Gln Asn | |
| 40 45 50 | |
| atc acc atc agc cag tat gct tgc cat gac caa gtg gca gtc acc att | 288 |
| Ile Thr Ile Ser Gln Tyr Ala Cys His Asp Gln Val Ala Val Thr Ile | |
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| ctt tgg tcc cca ggg gcc ctc ggc atc gaa ttc ctg aaa gga ttt cg | 336 |
| Leu Trp Ser Pro Gly Ala Leu Gly Ile Glu Phe Leu Lys Gly Phe Arg | |
| 70 75 80 85 | |
| gta ata ctg gag gag ctg aag tcg gag gga aga cag tgc caa caa ctg | 384 |
| Val Ile Leu Glu Glu Leu Lys Ser Glu Gly Arg Gln Cys Gln Gln Leu | |
| 90 95 100 | |
| att cta aag gat ccg aag cag ctc aac agt agc ttc aaa aga act gga | 432 |
| Ile Leu Lys Asp Pro Lys Gln Leu Asn Ser Ser Phe Lys Arg Thr Gly | |
| 105 110 115 | |
| atg gaa tct caa cct ttc ctg aat atg aaa ttt gaa acg gat tat ttc | 480 |
| Met Glu Ser Gln Pro Phe Leu Asn Met Lys Phe Glu Thr Asp Tyr Phe | |
| 120 125 130 | |
| gta aag gtt gtc cct ttt cct tcc att aaa aac gaa agc aat tac cac | 528 |
| Val Lys Val Val Pro Phe Pro Ser Ile Lys Asn Glu Ser Asn Tyr His | |
| 135 140 145 | |
| cct ttc ttc ttt aga acc cga gcc tgt gac ctg ttg tta cag ccg gac | 576 |
| Pro Phe Phe Arg Thr Arg Ala Cys Asp Leu Leu Leu Gln Pro Asp | |
| 150 155 160 165 | |
| aat cta gct tgt aaa ccc ttc tgg aag cct ccg aac ctg aac atc agc | 624 |
| Asn Leu Ala Cys Lys Pro Phe Trp Lys Pro Arg Asn Leu Asn Ile Ser | |
| 170 175 180 | |
| cag cat ggc tcg gac atg cag gtg tcc ttc gac cat gca ccg cac aac | 672 |
| Gln His Gly Ser Asp Met Gln Val Ser Phe Asp His Ala Pro His Asn | |
| 185 190 195 | |
| ttc ggc ttc cgt ttc tat ctt cac tac aag ctc aag cac gaa gga | 720 |
| Phe Gly Phe Arg Phe Phe Tyr Leu His Tyr Lys Leu Lys His Glu Gly | |
| 200 205 210 | |
| cct ttc aag cga aag acc tgt aag cag gag caa act aca gag acg acc | 768 |
| Pro Phe Lys Arg Lys Thr Cys Lys Gln Glu Gln Thr Thr Glu Thr Thr | |
| 215 220 225 | |

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| agc tgc ctc ctt caa aat gtt tct cca ggg gat tat ata att gag ctg Ser Cys Leu Leu Gln Asn Val Ser Pro Gly Asp Tyr Ile Ile Glu Leu 230 235 240 245 | 816 |
| gtg gat gac act aac aca aca aga aaa gtg atg cat tat gcc tta aag Val Asp Asp Thr Asn Thr Thr Arg Lys Val Met His Tyr Ala Leu Lys 250 255 260 | 864 |
| cca gtg cac tcc ccg tgg gcc ggg ccc atc aga gcc gtg gcc atc aca Pro Val His Ser Pro Trp Ala Gly Pro Ile Arg Ala Val Ala Ile Thr 265 270 275 | 912 |
| gtg cca ctg gta gtc ata tcg gca ttc gcg acg ctc ttc act gtg atg Val Pro Leu Val Val Ile Ser Ala Phe Ala Thr Leu Phe Thr Val Met 280 285 290 | 960 |
| tgc cgc aag aag caa caa gaa aat ata tat tca cat tta gat gaa gag Cys Arg Lys Lys Gln Gln Glu Asn Ile Tyr Ser His Leu Asp Glu Glu 295 300 305 | 1008 |
| agc tct gag tct tcc aca tac act gca gca ctc cca aga gag agg ctc Ser Ser Glu Ser Ser Thr Tyr Thr Ala Ala Leu Pro Arg Glu Arg Leu 310 315 320 325 | 1056 |
| cg ^g ccg ccg ccg aag gtc ttt ctc tgc tat tcc agt aaa gat ggc cag Arg Pro Arg Pro Lys Val Phe Leu Cys Tyr Ser Ser Lys Asp Gly Gln 330 335 340 | 1104 |
| aat cac atg aat gtc gtc cag tgt ttc gcc tac ttc ctc cag gac ttc Asn His Met Asn Val Val Gln Cys Phe Ala Tyr Phe Leu Gln Asp Phe 345 350 355 | 1152 |
| tgt ggc tgt gag gtg gct ctg gac ctg tgg gaa gac ttc agc ctc tgt Cys Gly Cys Glu Val Ala Leu Asp Leu Trp Glu Asp Phe Ser Leu Cys 360 365 370 | 1200 |
| aga gaa ggg cag aga gaa tgg gtc atc cag aag atc cac gag tcc cag Arg Glu Gly Gln Arg Glu Trp Val Ile Gln Lys Ile His Glu Ser Gln 375 380 385 | 1248 |
| ttc atc att gtg gtt tgt tcc aaa ggt atg aag tac ttt gtg gac aag Phe Ile Ile Val Val Cys Ser Lys Gly Met Lys Tyr Phe Val Asp Lys 390 395 400 405 | 1296 |
| aag aac tac aaa cac aaa gga ggt ggc cga ggc tcg ggg aaa gga gag Lys Asn Tyr Lys His Lys Gly Gly Arg Gly Ser Gly Lys Gly Glu 410 415 420 | 1344 |
| ctc ttc ctg gtg gcg gtg tca gcc att gcc gaa aag ctc cgc cag gcc Leu Phe Leu Val Ala Val Ser Ala Ile Ala Glu Lys Leu Arg Gln Ala 425 430 435 | 1392 |

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| aag cag agt tcg tcc gcg gcg ctc agc aag ttt atc gcc gtc tac ttt | 1440 |
| Lys Gln Ser Ser Ser Ala Ala Leu Ser Lys Phe Ile Ala Val Tyr Phe | |
| 440 445 450 | |
| gat tat tcc tgc gag gga gac gtc ccc ggt atc cta gac ctg agt acc | 1488 |
| Asp Tyr Ser Cys Glu Gly Asp Val Pro Gly Ile Leu Asp Leu Ser Thr | |
| 455 460 465 | |
| aag tac aga ctc atg gac aat ctt tcc tca gct ctg ttc cca ctc tgc | 1536 |
| Lys Tyr Arg Leu Met Asp Asn Leu Ser Ser Ala Leu Phe Pro Leu Cys | |
| 470 475 480 485 | |
| act ccc gag acc acg gcc tcc agg agc cgg ggc atg cac acg cga cag | 1584 |
| Thr Pro Glu Thr Thr Ala Ser Arg Ser Arg Gly Met His Thr Arg Gln | |
| 490 495 500 | |
| ggc agg gag aag gaa cta ctt ccg gag caa gtc agg ccg gtc cct ata | 1632 |
| Gly Arg Glu Lys Glu Leu Leu Pro Glu Gln Val Arg Pro Val Pro Ile | |
| 505 510 515 | |
| cgt cgc cat ttg caa cat gca cca gtt tat tgacgaggag cccgactgg | 1682 |
| Arg Arg His Leu Gln His Ala Pro Val Tyr | |
| 520 525 | |
| tcgaaaaagca gttcgcccc ttccatcctc ctccactgcg ctaccggag ccagtcttgg | 1742 |
| agaaaatttga ttccggcctt gttttaaatg atgtcatgtg caaaccaggg cctgagatgt | 1802 |
| acttctgcct aaaggttagag gcggctgttc ttggggcaac cggaccagcc gactcccagc | 1862 |
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-10 -5 -1 1 5

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10 15 20

Arg Asn Ser Gly Leu Tyr Asn Ile Thr Phe Lys Tyr Asp Asn Cys Thr
25 30 35

Thr Tyr Leu Asn Pro Val Gly Lys His Val Ile Ala Asp Ala Gln Asn
40 45 50

Ile Thr Ile Ser Gln Tyr Ala Cys His Asp Gln Val Ala Val Thr Ile
55 60 65

Leu Trp Ser Pro Gly Ala Leu Gly Ile Glu Phe Leu Lys Gly Phe Arg
70 75 80 85

Val Ile Leu Glu Glu Leu Lys Ser Glu Gly Arg Gln Cys Gln Gln Leu
90 95 100

Ile Leu Lys Asp Pro Lys Gln Leu Asn Ser Ser Phe Lys Arg Thr Gly
105 110 115

Met Glu Ser Gln Pro Phe Leu Asn Met Lys Phe Glu Thr Asp Tyr Phe
120 125 130

Val Lys Val Val Pro Phe Pro Ser Ile Lys Asn Glu Ser Asn Tyr His
135 140 145

Pro Phe Phe Phe Arg Thr Arg Ala Cys Asp Leu Leu Leu Gln Pro Asp
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Asn Leu Ala Cys Lys Pro Phe Trp Lys Pro Arg Asn Leu Asn Ile Ser
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Gln His Gly Ser Asp Met Gln Val Ser Phe Asp His Ala Pro His Asn
185 190 195

Phe Gly Phe Arg Phe Phe Tyr Leu His Tyr Lys Leu Lys His Glu Gly
200 205 210

Pro Phe Lys Arg Lys Thr Cys Lys Gln Glu Gln Thr Thr Glu Thr Thr
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Ser Cys Leu Leu Gln Asn Val Ser Pro Gly Asp Tyr Ile Ile Glu Leu
230 235 240 245

Val Asp Asp Thr Asn Thr Arg Lys Val Met His Tyr Ala Leu Lys
250 255 260

Pro Val His Ser Pro Trp Ala Gly Pro Ile Arg Ala Val Ala Ile Thr
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Val Pro Leu Val Val Ile Ser Ala Phe Ala Thr Leu Phe Thr Val Met
280 285 290

Cys Arg Lys Lys Gln Gln Glu Asn Ile Tyr Ser His Leu Asp Glu Glu
295 300 305

Ser Ser Glu Ser Ser Thr Tyr Thr Ala Ala Leu Pro Arg Glu Arg Leu
310 315 320 325

Arg Pro Arg Pro Lys Val Phe Leu Cys Tyr Ser Ser Lys Asp Gly Gln
330 335 340

Asn His Met Asn Val Val Gln Cys Phe Ala Tyr Phe Leu Gln Asp Phe
345 350 355

Cys Gly Cys Glu Val Ala Leu Asp Leu Trp Glu Asp Phe Ser Leu Cys
360 365 370

Arg Glu Gly Gln Arg Glu Trp Val Ile Gln Lys Ile His Glu Ser Gln
375 380 385

Phe Ile Ile Val Val Cys Ser Lys Gly Met Lys Tyr Phe Val Asp Lys
390 395 400 405

Lys Asn Tyr Lys His Lys Gly Gly Arg Gly Ser Gly Lys Gly Glu
410 415 420

Leu Phe Leu Val Ala Val Ser Ala Ile Ala Glu Lys Leu Arg Gln Ala
425 430 435

Lys Gln Ser Ser Ser Ala Ala Leu Ser Lys Phe Ile Ala Val Tyr Phe
440 445 450

Asp Tyr Ser Cys Glu Gly Asp Val Pro Gly Ile Leu Asp Leu Ser Thr
455 460 465

Lys Tyr Arg Leu Met Asp Asn Leu Ser Ser Ala Leu Phe Pro Leu Cys
470 475 480 485

Thr Pro Glu Thr Thr Ala Ser Arg Ser Arg Gly Met His Thr Arg Gln
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 Met Glu Gly Ala Gly
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ccc cgg ggg gcc ggg ccg gcg cgg cgc cgg gga gcc ggg ggg ccc ccc 224
 Pro Arg Gly Ala Gly Pro Ala Arg Arg Arg Gly Ala Gly Gly Pro Pro
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 Ser Pro Leu Leu Pro Ser Leu Leu Leu Leu Leu Leu Leu Trp Met Leu
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cag caa ggg gac gag tgt ggg att gcg gtg tgc gaa ggc aac tcc acg 416
 Gln Gln Gly Asp Glu Cys Gly Ile Ala Val Cys Glu Gly Asn Ser Thr
 35 40 45

tgc tca gag aac gag gtg tgc gtg agg cct ggc gag tgc cgc tgc cgc 464
 Cys Ser Glu Asn Glu Val Cys Val Arg Pro Gly Glu Cys Arg Cys Arg
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cac ggc tac ttc ggt gcc aac tgc gac acc aag tgc ccc cgc cag ttc 512
 His Gly Tyr Phe Gly Ala Asn Cys Asp Thr Lys Cys Pro Arg Gln Phe
 65 70 75

tgg ggc ccc gac tgc aag gag ctg tgt agc tgc cac cca cac ggg cag 560
 Trp Gly Pro Asp Cys Lys Glu Leu Cys Ser Cys His Pro His Gly Gln
 80 85 90

tgc gag gac gtg aca ggc cag tgt act tgt cac gcg cgg cgc tgg ggc 608
 Cys Glu Asp Val Thr Gly Gln Cys Thr Cys His Ala Arg Arg Trp Gly
 95 100 105 110

gcg cgc tgc gag cat gcg tgc cag tgc cag cac ggc acg tgc cac ccc 656

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| 115 | 120 | 125 | |
| cgg agc ggc gcg tgc cgc tgt gag ccc ggc ccc gcc cct ccg ctc aga | | | 704 |
| Arg Ser Gly Ala Cys Arg Cys Glu Pro Gly Pro Ala Pro Pro Leu Arg | | | |
| 130 | 135 | 140 | |
| ccc cgc ccc cgc agg gag ctt tcg ctt ggg agg aag aag gcg ccg cac | | | 752 |
| Pro Arg Pro Arg Arg Glu Leu Ser Leu Gly Arg Lys Lys Ala Pro His | | | |
| 145 | 150 | 155 | |
| cga cta tgc ggg cgc ttc agt cgc atc agc atg aag ctg ccc cgg atc | | | 800 |
| Arg Leu Cys Gly Arg Phe Ser Arg Ile Ser Met Lys Leu Pro Arg Ile | | | |
| 160 | 165 | 170 | |
| ccg ctc cgg agg cag aaa cta ccc aaa gtc gta ggt aag gat gac agc | | | 848 |
| Pro Leu Arg Arg Gln Lys Leu Pro Lys Val Val Gly Lys Asp Asp Ser | | | |
| 175 | 180 | 185 | 190 |
| gcg ggg gat ctg gga gaa aca cct ctc gac gca gga agc tgc tgg gaa | | | 896 |
| Ala Gly Asp Leu Gly Glu Thr Pro Leu Asp Ala Gly Ser Cys Trp Glu | | | |
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| -20 | -15 | -10 | |
| Leu Leu Trp Met Leu Pro Asp Thr Val Ala Pro Gln Glu Leu Asn Pro | | | |
| -5 | -1 | 1 | 5 |
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| 10 | 15 | 20 | 25 |

Cys Ala Gly Trp Arg Gln Gln Gly Asp Glu Cys Gly Ile Ala Val Cys
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Glu Gly Asn Ser Thr Cys Ser Glu Asn Glu Val Cys Val Arg Pro Gly
45 50 55

Glu Cys Arg Cys Arg His Gly Tyr Phe Gly Ala Asn Cys Asp Thr Lys
60 65 70

Cys Pro Arg Gln Phe Trp Gly Pro Asp Cys Lys Glu Leu Cys Ser Cys
75 80 85

His Pro His Gly Gln Cys Glu Asp Val Thr Gly Gln Cys Thr Cys His
90 95 100 105

Ala Arg Arg Trp Gly Ala Arg Cys Glu His Ala Cys Gln Cys Gln His
110 115 120

Gly Thr Cys His Pro Arg Ser Gly Ala Cys Arg Cys Glu Pro Gly Pro
125 130 135

Ala Pro Pro Leu Arg Pro Arg Pro Arg Arg Glu Leu Ser Leu Gly Arg
140 145 150

Lys Lys Ala Pro His Arg Leu Cys Gly Arg Phe Ser Arg Ile Ser Met
155 160 165

Lys Leu Pro Arg Ile Pro Leu Arg Arg Gln Lys Leu Pro Lys Val Val
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 Glu Glu Leu Val Leu Ala Leu Arg Ser Glu Glu Asp Gly Leu Ala Glu
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gca ccc gag cac gga acc aca gcc acc ttc cac cgc tgc gcc aag gat 248
 Ala Pro Glu His Gly Thr Ala Thr Phe His Arg Cys Ala Lys Asp
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ccg tgg agg ttg cct ggc acc tac gtg gtg ctg aag gag gag acc 296
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 120 125 130

gcc cag agc atc ccg tgg aac ctg gag cgg att acc cct cca cgg tac 536
 Ala Gln Ser Ile Pro Trp Asn Leu Glu Arg Ile Thr Pro Pro Arg Tyr
 135 140 145

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| 150 | 155 | 160 | |
| tat ctc cta gac acc agc ata cag agt gac cac cgg gaa atc gag ggc | | | 632 |
| Tyr Leu Leu Asp Thr Ser Ile Gln Ser Asp His Arg Glu Ile Glu Gly | | | |
| 165 | 170 | 175 | 180 |
| agg gtc atg gtc acc gac ttc gag aat gtg ccc gag gag gac ggg acc | | | 680 |
| Arg Val Met Val Thr Asp Phe Glu Asn Val Pro Glu Glu Asp Gly Thr | | | |
| 185 | 190 | 195 | |
| cgc ttc cac aga cag gcc agc aag tgt gac agt cat ggc acc cac ctg | | | 728 |
| Arg Phe His Arg Gln Ala Ser Lys Cys Asp Ser His Gly Thr His Leu | | | |
| 200 | 205 | 210 | |
| gca ggg gtg gtc agc ggc cgg gat gcc ggc gtg gcc aag ggt gcc agc | | | 776 |
| Ala Gly Val Val Ser Gly Arg Asp Ala Gly Val Ala Lys Gly Ala Ser | | | |
| 215 | 220 | 225 | |
| atg cgc agc ctg cgc gtg ctc aac tgc caa ggg aag ggc acg gtt agc | | | 824 |
| Met Arg Ser Leu Arg Val Leu Asn Cys Gln Gly Lys Gly Thr Val Ser | | | |
| 230 | 235 | 240 | |
| ggc acc ctc ata ggc ctg gag ttt att cgg aaa agc cag ctg gtc cag | | | 872 |
| Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg Lys Ser Gln Leu Val Gln | | | |
| 245 | 250 | 255 | 260 |
| cct gtg ggg cca ctg gtg ctg ctg ccc ctg gcg ggt ggg tac agc | | | 920 |
| Pro Val Gly Pro Leu Val Val Leu Leu Pro Leu Ala Gly Gly Tyr Ser | | | |
| 265 | 270 | 275 | |
| cgc gtc ctc aac gcc gcc tgc cag cgc ctg gcg agg gct ggg gtc gtg | | | 968 |
| Arg Val Leu Asn Ala Ala Cys Gln Arg Leu Ala Arg Ala Gly Val Val | | | |
| 280 | 285 | 290 | |
| ctg gtc acc gct gcc ggc aac ttc cgg gac gat gcc tgc ctc tac tcc | | | 1016 |
| Leu Val Thr Ala Ala Gly Asn Phe Arg Asp Asp Ala Cys Leu Tyr Ser | | | |
| 295 | 300 | 305 | |
| cca gcc tca gct ccc gag gtc atc aca gtt ggg gcc acc aat gcc cag | | | 1064 |
| Pro Ala Ser Ala Pro Glu Val Ile Thr Val Gly Ala Thr Asn Ala Gln | | | |
| 310 | 315 | 320 | |
| gac cag ccg gtg acc ctg ggg act ttg ggg acc aac ttt ggc cgc tgt | | | 1112 |
| Asp Gln Pro Val Thr Leu Gly Thr Leu Gly Thr Asn Phe Gly Arg Cys | | | |
| 325 | 330 | 335 | 340 |
| gtg gac ctc ttt gcc cca ggg gag gac atc att ggt gcc tcc agc gac | | | 1160 |
| Val Asp Leu Phe Ala Pro Gly Glu Asp Ile Ile Gly Ala Ser Ser Asp | | | |
| 345 | 350 | 355 | |
| tgc agc acc tgc ttt gtg tca cag agt ggg aca tca cag gct gct gcc | | | 1208 |
| Cys Ser Thr Cys Phe Val Ser Gln Ser Gly Thr Ser Gln Ala Ala Ala | | | |
| 360 | 365 | 370 | |

| | |
|---|------|
| cac gtg gct ggc att gca gcc atg atg ctg tct gcc gag ccg gag ctc | 1256 |
| His Val Ala Gly Ile Ala Ala Met Met Leu Ser Ala Glu Pro Glu Leu | |
| 375 380 385 | |
| acc ctg gcc gag ttg agg cag aga ctg atc cac ttc tct gcc aaa gat | 1304 |
| Thr Leu Ala Glu Leu Arg Gln Arg Leu Ile His Phe Ser Ala Lys Asp | |
| 390 395 400 | |
| gtc atc aat gag gcc tgg ttc cct gag gac cag ccg gta ctg acc ccc | 1352 |
| Val Ile Asn Glu Ala Trp Phe Pro Glu Asp Gln Arg Val Leu Thr Pro | |
| 405 410 415 420 | |
| aac ctg gtg gcc gcc ctg ccc ccc agc acc cat ggg gca ggt tgg cag | 1400 |
| Asn Leu Val Ala Ala Leu Pro Pro Ser Thr His Gly Ala Gly Trp Gln | |
| 425 430 435 | |
| ctg ttt tgc agg act gtg tgg tca gca cac tcg ggg cct aca ccg atg | 1448 |
| Leu Phe Cys Arg Thr Val Trp Ser Ala His Ser Gly Pro Thr Arg Met | |
| 440 445 450 | |
| gcc aca gcc atc gcc cgc tgc gcc cca gat gag gag ctg ctg agc tgc | 1496 |
| Ala Thr Ala Ile Ala Arg Cys Ala Pro Asp Glu Leu Leu Ser Cys | |
| 455 460 465 | |
| tcc agt ttc tcc agg agt ggg aag cgg cgg ggc gag cgc atg gag gcc | 1544 |
| Ser Ser Phe Ser Arg Ser Gly Lys Arg Arg Gly Glu Arg Met Glu Ala | |
| 470 475 480 | |
| caa ggg ggc aag ctg gtc tgc cgg gcc cac aac gct ttt ggg ggt gag | 1592 |
| Gln Gly Gly Lys Leu Val Cys Arg Ala His Asn Ala Phe Gly Gly Glu | |
| 485 490 495 500 | |
| ggt gtc tac gcc att gcc agg tgc tgc ctg cta ccc cag gcc aac tgc | 1640 |
| Gly Val Tyr Ala Ile Ala Arg Cys Cys Leu Leu Pro Gln Ala Asn Cys | |
| 505 510 515 | |
| agc gtc cac aca gct cca cca gct gag gcc agc atg ggg acc cgt gtc | 1688 |
| Ser Val His Thr Ala Pro Pro Ala Glu Ala Ser Met Gly Thr Arg Val | |
| 520 525 530 | |
| cac tgc cac caa cag ggc cac gtc ctc aca ggc tgc agc tcc cac tgg | 1736 |
| His Cys His Gln Gln Gly His Val Leu Thr Gly Cys Ser Ser His Trp | |
| 535 540 545 | |
| gag gtg gag gac ctt ggc acc cac aag ccg cct gtg ctg agg cca cga | 1784 |
| Glu Val Glu Asp Leu Gly Thr His Lys Pro Pro Val Leu Arg Pro Arg | |
| 550 555 560 | |
| ggt cag ccc aac cag tgc gtg ggc cac agg gag gcc agc atc cac gct | 1832 |
| Gly Gln Pro Asn Gln Cys Val Gly His Arg Glu Ala Ser Ile His Ala | |
| 565 570 575 580 | |

| | |
|---|------|
| tcc tgc tgc cat gcc cca ggt ctg gaa tgc aaa gtc aag gag cat gga | 1880 |
| Ser Cys Cys His Ala Pro Gly Leu Glu Cys Lys Val Lys Glu His Gly | |
| 585 590 595 | |
| atc ccg gcc cct cag gag cag gtg acc gtg gcc tgc gag gag ggc tgg | 1928 |
| Ile Pro Ala Pro Gln Glu Gln Val Thr Val Ala Cys Glu Glu Gly Trp | |
| 600 605 610 | |
| acc ctg act ggc tgc agt gcc ctc cct ggg acc tcc cac gtc ctg ggg | 1976 |
| Thr Leu Thr Gly Cys Ser Ala Leu Pro Gly Thr Ser His Val Leu Gly | |
| 615 620 625 | |
| gcc tac gcc gta gac aac acg tgt gta gtc agg agc cgg gac gtc agc | 2024 |
| Ala Tyr Ala Val Asp Asn Thr Cys Val Val Arg Ser Arg Asp Val Ser | |
| 630 635 640 | |
| act aca ggc agc acc agc gaa gag gcc gtg aca gcc gtt gcc atc tgc | 2072 |
| Thr Thr Gly Ser Thr Ser Glu Glu Ala Val Thr Ala Val Ala Ile Cys | |
| 645 650 655 660 | |
| tgc cgg agc cgg cac ctg gcg cag gcc ttc cag gag ctc cag | 2114 |
| Cys Arg Ser Arg His Leu Ala Gln Ala Phe Gln Glu Leu Gln | |
| 665 670 | |
| tgacagcccc atcccaggat gggtgtctgg ggagggtcaa gggctggggc tgagctttaa | 2174 |
| aatggttccg acttgtccct ctctcagccc ttcatg | 2210 |
| <210> 20 | |
| <211> 692 | |
| <212> PRT | |
| <213> Homo sapiens | |
| <400> 20 | |
| Met Gly Thr Val Ser Ser Arg Arg Ser Trp Trp Pro Leu Pro Leu Leu | |
| -15 -10 -5 | |
| Leu Leu Leu Leu Leu Leu Gly Pro Ala Gly Ala Arg Ala Gln Glu | |
| -1 1 5 10 | |
| Asp Glu Asp Gly Asp Tyr Glu Glu Leu Val Leu Ala Leu Arg Ser Glu | |
| 15 20 25 30 | |
| Glu Asp Gly Leu Ala Glu Ala Pro Glu His Gly Thr Thr Ala Thr Phe | |
| 35 40 45 | |
| His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro Gly Thr Tyr Val Val | |
| 50 55 60 | |

Val Leu Lys Glu Glu Thr His Leu Ser Gln Ser Glu Arg Thr Ala Arg
65 70 75

Arg Leu Gln Ala Gln Ala Ala Arg Arg Gly Tyr Leu Thr Lys Ile Leu
80 85 90

His Val Phe His Gly Leu Leu Pro Gly Phe Leu Val Lys Met Ser Gly
95 100 105 110

Asp Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile Glu
115 120 125

Glu Asp Ser Ser Val Phe Ala Gln Ser Ile Pro Trp Asn Leu Glu Arg
130 135 140

Ile Thr Pro Pro Arg Tyr Arg Ala Asp Glu Tyr Gln Pro Pro Asp Gly
145 150 155

Gly Ser Leu Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln Ser Asp
160 165 170

His Arg Glu Ile Glu Gly Arg Val Met Val Thr Asp Phe Glu Asn Val
175 180 185 190

Pro Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys Cys Asp
195 200 205

Ser His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp Ala Gly
210 215 220

Val Ala Lys Gly Ala Ser Met Arg Ser Leu Arg Val Leu Asn Cys Gln
225 230 235

Gly Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg
240 245 250

Lys Ser Gln Leu Val Gln Pro Val Gly Pro Leu Val Val Leu Leu Pro
255 260 265 270

Leu Ala Gly Gly Tyr Ser Arg Val Leu Asn Ala Ala Cys Gln Arg Leu
275 280 285

Ala Arg Ala Gly Val Val Leu Val Thr Ala Ala Gly Asn Phe Arg Asp
290 295 300

Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val
305 310 315

Gly Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly
320 325 330

Thr Asn Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Glu Asp Ile
335 340 345 350

Ile Gly Ala Ser Ser Asp Cys Ser Thr Cys Phe Val Ser Gln Ser Gly
355 360 365

Thr Ser Gln Ala Ala Ala His Val Ala Gly Ile Ala Ala Met Met Leu
370 375 380

Ser Ala Glu Pro Glu Leu Thr Leu Ala Glu Leu Arg Gln Arg Leu Ile
385 390 395

His Phe Ser Ala Lys Asp Val Ile Asn Glu Ala Trp Phe Pro Glu Asp
400 405 410

Gln Arg Val Leu Thr Pro Asn Leu Val Ala Ala Leu Pro Pro Ser Thr
415 420 425 430

His Gly Ala Gly Trp Gln Leu Phe Cys Arg Thr Val Trp Ser Ala His
435 440 445

Ser Gly Pro Thr Arg Met Ala Thr Ala Ile Ala Arg Cys Ala Pro Asp
450 455 460

Glu Glu Leu Leu Ser Cys Ser Ser Phe Ser Arg Ser Gly Lys Arg Arg
465 470 475

Gly Glu Arg Met Glu Ala Gln Gly Gly Lys Leu Val Cys Arg Ala His
480 485 490

Asn Ala Phe Gly Gly Glu Gly Val Tyr Ala Ile Ala Arg Cys Cys Leu
495 500 505 510

o Leu Pro Gln Ala Asn Cys Ser Val His Thr Ala Pro Pro Ala Glu Ala
515 520 525

Ser Met Gly Thr Arg Val His Cys His Gln Gln Gly His Val Leu Thr
530 535 540

Gly Cys Ser Ser His Trp Glu Val Glu Asp Leu Gly Thr His Lys Pro
545 550 555

Pro Val Leu Arg Pro Arg Gly Gln Pro Asn Gln Cys Val Gly His Arg
560 565 570

Glu Ala Ser Ile His Ala Ser Cys Cys His Ala Pro Gly Leu Glu Cys
575 580 585 590

Lys Val Lys Glu His Gly Ile Pro Ala Pro Gln Glu Gln Val Thr Val
595 600 605

Ala Cys Glu Glu Gly Trp Thr Leu Thr Gly Cys Ser Ala Leu Pro Gly
610 615 620

Thr Ser His Val Leu Gly Ala Tyr Ala Val Asp Asn Thr Cys Val Val
625 630 635

Arg Ser Arg Asp Val Ser Thr Thr Gly Ser Thr Ser Glu Glu Ala Val
640 645 650

Thr Ala Val Ala Ile Cys Cys Arg Ser Arg His Leu Ala Gln Ala Phe
655 660 665 670

Gln Glu Leu Gln

<210> 21
 <211> 2492
 <212> DNA
 <213> Homo sapiens

 <220>
 <221> CDS
 <222> (322)..(2379)

 <220>
 <221> mat_peptide
 <222> (376)..()

 <220>
 <221> variation
 <222> (2484)..(2484)
 <223> wherein n is A, G, C, or T

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 ggccttcaa agtgtgcagt tgtctcctcc ctgtccagcc ccatcgctgc ccaggaccag 60
 ctgggccccg gtctgacccctg aggctgctgc tcagcgccgg ggcgctggcg ctctccattc
 gagcacccctc cagcataccg ctccggctccg ggagccgctc tgcaaagttg ggcagctcag 120
 agcgcaagct ttgcctctcg acttctccct ccttgggtcc ccggccccc cgcctccac
 gatcccttcc actaggagca gccagtccttca gcgggctggc aacttgcacc ctttccttagt 180
 catcctccct gaaacgcgac c atg ctg tta agg ggc gtc ctc ctg gcg ttg 240
 Met Leu Leu Arg Gly Val Leu Leu Ala Leu
 -15 -10

 caa gcc ctg cag ctc gcc ggt gcc ctc gac ctg ccc gct ggg tcc tgc 300
 Gln Ala Leu Gln Leu Ala Gly Ala Leu Asp Leu Pro Ala Gly Ser Cys 351
 -5 -1 1 5

 gcc ttt gaa gag agc act tgc ggc ttt gac tcc gtg ttg gcc tct ctg 399
 Ala Phe Glu Glu Ser Thr Cys Gly Phe Asp Ser Val Leu Ala Ser Leu 447
 10 15 20

 ccg tgg att tta aat gag gaa ggc cat tac att tat gtg gat acc tcc 495
 Pro Trp Ile Leu Asn Glu Glu Gly His Tyr Ile Tyr Val Asp Thr Ser
 25 30 35 40

 ttt ggc aag cag ggg gag aaa gct gtg ctg cta agt cct gac tta cag 543
 Phe Gly Lys Gln Gly Glu Lys Ala Val Leu Leu Ser Pro Asp Leu Gln
 45 50 55

 gct gag gaa tgg agc tgc ctc cgt ttg gtc tac cag ata acc aca tct 591
 Ala Glu Glu Trp Ser Cys Leu Arg Leu Val Tyr Gln Ile Thr Thr Ser
 60 65 70

| | |
|---|------|
| tcg gag tct ctg tca gat ccc agc cag ctg aac ctc tac atg aga ttt | 639 |
| Ser Glu Ser Leu Ser Asp Pro Ser Gln Leu Asn Leu Tyr Met Arg Phe | |
| 75 80 85 | |
| gaa gat gaa agc ttt gat cgc ttg ctt tgg tca gct aag gaa cct tca | 687 |
| Glu Asp Glu Ser Phe Asp Arg Leu Leu Trp Ser Ala Lys Glu Pro Ser | |
| 90 95 100 | |
| gac agc tgg ctc ata gcc agc ttg gat ttg caa aac agt tcc aag aaa | 735 |
| Asp Ser Trp Leu Ile Ala Ser Leu Asp Leu Gln Asn Ser Ser Lys Lys | |
| 105 110 115 120 | |
| ttc aag att tta ata gaa ggt gta cta gga cag gga aac aca gcc agc | 783 |
| Phe Lys Ile Leu Ile Glu Gly Val Leu Gly Gln Gly Asn Thr Ala Ser | |
| 125 130 135 | |
| atc gca cta ttt gaa atc aag atg aca acc ggc tac tgt att gaa tgt | 831 |
| Ile Ala Leu Phe Glu Ile Lys Met Thr Thr Gly Tyr Cys Ile Glu Cys | |
| 140 145 150 | |
| gac ttt gaa gaa aat cat ctc tgt ggc ttt gtg aac cgc tgg aat ccc | 879 |
| Asp Phe Glu Glu Asn His Leu Cys Gly Phe Val Asn Arg Trp Asn Pro | |
| 155 160 165 | |
| aat gtg aac tgg ttt gtt gga gga gga agt att cgg aat gtc cac tcc | 927 |
| Asn Val Asn Trp Phe Val Gly Gly Ser Ile Arg Asn Val His Ser | |
| 170 175 180 | |
| att ctc cca cag gat cac acc ttc aag agt gaa ctg ggc cac tac atg | 975 |
| Ile Leu Pro Gln Asp His Thr Phe Lys Ser Glu Leu Gly His Tyr Met | |
| 185 190 195 200 | |
| tac gtg gac tca gtt tat gtg aag cac ttc cag gag gtg gca cag ctc | 1023 |
| Tyr Val Asp Ser Val Tyr Val Lys His Phe Gln Glu Val Ala Gln Leu | |
| 205 210 215 | |
| atc tcc ccg ttg acc acg gcc ccc atg gct ggc tgc ctg tca ttt tat | 1071 |
| Ile Ser Pro Leu Thr Thr Ala Pro Met Ala Gly Cys Leu Ser Phe Tyr | |
| 220 225 230 | |
| tac cag atc cag cag ggg aat gac aat gtc ttt tcc ctt tac act cgg | 1119 |
| Tyr Gln Ile Gln Gln Gly Asn Asn Val Phe Ser Leu Tyr Thr Arg | |
| 235 240 245 | |
| gat gtg gct ggc ctt tac gag gaa atc tgg aaa gca gac agg cca ggg | 1167 |
| Asp Val Ala Gly Leu Tyr Glu Glu Ile Trp Lys Ala Asp Arg Pro Gly | |
| 250 255 260 | |
| aat gct gcc tgg aac ctt gcg gag gtc gag ttc aat gct cct tac ccc | 1215 |
| Asn Ala Ala Trp Asn Leu Ala Glu Val Glu Phe Asn Ala Pro Tyr Pro | |
| 265 270 275 280 | |
| atg gag gtt att ttt gaa gtt gct ttc aat ggt ccc aag gga ggt tat | 1263 |
| Met Glu Val Ile Phe Glu Val Ala Phe Asn Gly Pro Lys Gly Tyr | |

| 285 | 290 | 295 | |
|---|-----|-----|------|
| gtt gcc ctg gat gat att tca ttc tct cct gtt cac tgc cag aat cag Val Ala Leu Asp Asp Ile Ser Phe Ser Pro Val His Cys Gln Asn Gln 300 | 305 | 310 | 1311 |
| aca gaa ctt ctg ttc agt gcc gtg gaa gcc agc tgc aat ttt gag caa Thr Glu Leu Leu Phe Ser Ala Val Glu Ala Ser Cys Asn Phe Glu Gln 315 | 320 | 325 | 1359 |
| gat ctc tgc aac ttt tac caa gat aaa gaa ggt cca ggt tgg acc cga Asp Leu Cys Asn Phe Tyr Gln Asp Lys Glu Gly Pro Gly Trp Thr Arg 330 | 335 | 340 | 1407 |
| gtg aaa gta aaa cca aac atg tat cgg gct gga gac cac act aca ggc Val Lys Val Lys Pro Asn Met Tyr Arg Ala Gly Asp His Thr Thr Gly 345 | 350 | 355 | 1455 |
| tta ggg tat tac ctg cta gcc aac aca aag ttc aca tct cag cct ggc Leu Gly Tyr Tyr Leu Leu Ala Asn Thr Lys Phe Thr Ser Gln Pro Gly 365 | 370 | 375 | 1503 |
| tac att gga agg ctc tat ggg ccc tcc cta cca gga aac ttg cag tat Tyr Ile Gly Arg Leu Tyr Gly Pro Ser Leu Pro Gly Asn Leu Gln Tyr 380 | 385 | 390 | 1551 |
| tgt ctg cgt ttt cat tat gcc atc tat gga ttt tta aaa atg agt gac Cys Leu Arg Phe His Tyr Ala Ile Tyr Gly Phe Leu Lys Met Ser Asp 395 | 400 | 405 | 1599 |
| acc cta gca gtt tac atc ttt gaa gag aac cat gtg gtt caa gag aag Thr Leu Ala Val Tyr Ile Phe Glu Asn His Val Val Gln Glu Lys 410 | 415 | 420 | 1647 |
| atc tgg tct gtg ttg gag tcc cca agg ggt gtt tgg atg caa gct gaa Ile Trp Ser Val Leu Glu Ser Pro Arg Gly Val Trp Met Gln Ala Glu 425 | 430 | 435 | 1695 |
| atc acc ttt aag aag ccc atg cct acc aag gtg gtt ttc atg agc cta Ile Thr Phe Lys Lys Pro Met Pro Thr Lys Val Val Phe Met Ser Leu 445 | 450 | 455 | 1743 |
| tgc aaa agt ttc tgg gac tgt ggg ctt gta gcc ctg gat gac att aca Cys Lys Ser Phe Trp Asp Cys Gly Leu Val Ala Leu Asp Asp Ile Thr 460 | 465 | 470 | 1791 |
| ata caa ttg gga agc tgc tca tct tca gag aaa ctt cca cct cca cct Ile Gln Leu Gly Ser Cys Ser Ser Glu Lys Leu Pro Pro Pro 475 | 480 | 485 | 1839 |
| gga gag tgt act ttc gag caa gat gaa tgt aca ttt act cag gag aaa Gly Glu Cys Thr Phe Glu Gln Asp Glu Cys Thr Phe Thr Gln Glu Lys 490 | 495 | 500 | 1887 |

| | |
|---|------|
| aga aac cgg agc agc tgg cac agg agg gga gaa act ccc act tcc Arg Asn Arg Ser Ser Trp His Arg Arg Arg Gly Glu Thr Pro Thr Ser 505 510 515 520 | 1935 |
| tac aca gga cca aag gga gat cac act act ggg gta ggc tac tac atg Tyr Thr Gly Pro Lys Gly Asp His Thr Thr Gly Val Gly Tyr Tyr Met 525 530 535 | 1983 |
| tac att gag gcc tcc cat atg gtg tat gga caa aaa gca cgc ctc ttg Tyr Ile Glu Ala Ser His Met Val Tyr Gly Gln Lys Ala Arg Leu Leu 540 545 550 | 2031 |
| tcc agg cct ctg cga gga gtc tct gga aaa cac tgc ttg acc ttt ttc Ser Arg Pro Leu Arg Gly Val Ser Gly Lys His Cys Leu Thr Phe Phe 555 560 565 | 2079 |
| tac cac atg tat gga ggg ggc act ggc ctg ctg agt gtt tat ctg aaa Tyr His Met Tyr Gly Gly Thr Gly Leu Leu Ser Val Tyr Leu Lys 570 575 580 | 2127 |
| aag gaa gaa gac agt gaa gag tcc ctc tta tgg agg aga aga ggt gaa Lys Glu Glu Asp Ser Glu Glu Ser Leu Leu Trp Arg Arg Arg Gly Glu 585 590 595 600 | 2175 |
| cag agc att tcc tgg cta cga gca ctg att gaa tac agc tgt gag agg Gln Ser Ile Ser Trp Leu Arg Ala Leu Ile Glu Tyr Ser Cys Glu Arg 605 610 615 | 2223 |
| caa cac cag ata att ttt gaa gcc att cga gga gta tca ata aga agt Gln His Gln Ile Ile Phe Glu Ala Ile Arg Gly Val Ser Ile Arg Ser 620 625 630 | 2271 |
| gat att gcc att gat gat gtt aaa ttt cag gca gga ccc tgt gga gaa Asp Ile Ala Ile Asp Asp Val Lys Phe Gln Ala Gly Pro Cys Gly Glu 635 640 645 | 2319 |
| atg gaa gat aca act caa caa tca tca gga tat tct gag gac tta aat Met Glu Asp Thr Thr Gln Gln Ser Ser Gly Tyr Ser Glu Asp Leu Asn 650 655 660 | 2367 |
| gaa att gag tat taagaaatga tctgcattgg atttactaga cgaaaaaccat Glu Ile Glu Tyr 665 | 2419 |
| acctctcttc aatcaaaatg aaaacaaagc aatgaatac tggacagtct taacaattta | 2479 |
| taagntataa aat | 2492 |

<210> 22
<211> 686
<212> PRT
<213> Homo sapiens

<400> 22

Met Leu Leu Arg Gly Val Leu Leu Ala Leu Gln Ala Leu Gln Leu Ala
-15 -10 -5

Gly Ala Leu Asp Leu Pro Ala Gly Ser Cys Ala Phe Glu Glu Ser Thr
-1 1 5 10

Cys Gly Phe Asp Ser Val Leu Ala Ser Leu Pro Trp Ile Leu Asn Glu
15 20 25 30

Glu Gly His Tyr Ile Tyr Val Asp Thr Ser Phe Gly Lys Gln Gly Glu
35 40 45

Lys Ala Val Leu Leu Ser Pro Asp Leu Gln Ala Glu Glu Trp Ser Cys
50 55 60

Leu Arg Leu Val Tyr Gln Ile Thr Thr Ser Ser Glu Ser Leu Ser Asp
65 70 75

Pro Ser Gln Leu Asn Leu Tyr Met Arg Phe Glu Asp Glu Ser Phe Asp
80 85 90

Arg Leu Leu Trp Ser Ala Lys Glu Pro Ser Asp Ser Trp Leu Ile Ala
95 100 105 110

Ser Leu Asp Leu Gln Asn Ser Ser Lys Lys Phe Lys Ile Leu Ile Glu
115 120 125

Gly Val Leu Gly Gln Gly Asn Thr Ala Ser Ile Ala Leu Phe Glu Ile
130 135 140

Lys Met Thr Thr Gly Tyr Cys Ile Glu Cys Asp Phe Glu Glu Asn His
145 150 155

Leu Cys Gly Phe Val Asn Arg Trp Asn Pro Asn Val Asn Trp Phe Val
160 165 170

Gly Gly Gly Ser Ile Arg Asn Val His Ser Ile Leu Pro Gln Asp His
175 180 185 190

Thr Phe Lys Ser Glu Leu Gly His Tyr Met Tyr Val Asp Ser Val Tyr
195 200 205

Val Lys His Phe Gln Glu Val Ala Gln Leu Ile Ser Pro Leu Thr Thr
210 215 220

Ala Pro Met Ala Gly Cys Leu Ser Phe Tyr Tyr Gln Ile Gln Gln Gly
225 230 235

Asn Asp Asn Val Phe Ser Leu Tyr Thr Arg Asp Val Ala Gly Leu Tyr
240 245 250

Glu Glu Ile Trp Lys Ala Asp Arg Pro Gly Asn Ala Ala Trp Asn Leu
255 260 265 270

Ala Glu Val Glu Phe Asn Ala Pro Tyr Pro Met Glu Val Ile Phe Glu
275 280 285

Val Ala Phe Asn Gly Pro Lys Gly Gly Tyr Val Ala Leu Asp Asp Ile
290 295 300

Ser Phe Ser Pro Val His Cys Gln Asn Gln Thr Glu Leu Phe Ser
305 310 315

Ala Val Glu Ala Ser Cys Asn Phe Glu Gln Asp Leu Cys Asn Phe Tyr
320 325 330

Gln Asp Lys Glu Gly Pro Gly Trp Thr Arg Val Lys Val Lys Pro Asn
335 340 345 350

Met Tyr Arg Ala Gly Asp His Thr Thr Gly Leu Gly Tyr Tyr Leu Leu
355 360 365

Ala Asn Thr Lys Phe Thr Ser Gln Pro Gly Tyr Ile Gly Arg Leu Tyr
370 375 380

Gly Pro Ser Leu Pro Gly Asn Leu Gln Tyr Cys Leu Arg Phe His Tyr
385 390 395

Ala Ile Tyr Gly Phe Leu Lys Met Ser Asp Thr Leu Ala Val Tyr Ile
400 405 410

Phe Glu Glu Asn His Val Val Gln Glu Lys Ile Trp Ser Val Leu Glu
415 420 425 430

Ser Pro Arg Gly Val Trp Met Gln Ala Glu Ile Thr Phe Lys Lys Pro
435 440 445

Met Pro Thr Lys Val Val Phe Met Ser Leu Cys Lys Ser Phe Trp Asp
450 455 460

Cys Gly Leu Val Ala Leu Asp Asp Ile Thr Ile Gln Leu Gly Ser Cys
465 470 475

Ser Ser Ser Glu Lys Leu Pro Pro Pro Pro Gly Glu Cys Thr Phe Glu
480 485 490

Gln Asp Glu Cys Thr Phe Thr Gln Glu Lys Arg Asn Arg Ser Ser Trp
495 500 505 510

His Arg Arg Arg Gly Glu Thr Pro Thr Ser Tyr Thr Gly Pro Lys Gly
515 520 525

Asp His Thr Thr Gly Val Gly Tyr Tyr Met Tyr Ile Glu Ala Ser His
530 535 540

Met Val Tyr Gly Gln Lys Ala Arg Leu Leu Ser Arg Pro Leu Arg Gly
545 550 555

Val Ser Gly Lys His Cys Leu Thr Phe Phe Tyr His Met Tyr Gly Gly
560 565 570

Gly Thr Gly Leu Leu Ser Val Tyr Leu Lys Lys Glu Glu Asp Ser Glu
575 580 585 590

Glu Ser Leu Leu Trp Arg Arg Arg Gly Glu Gln Ser Ile Ser Trp Leu
595 600 605

Arg Ala Leu Ile Glu Tyr Ser Cys Glu Arg Gln His Gln Ile Ile Phe
 610 615 620

Glu Ala Ile Arg Gly Val Ser Ile Arg Ser Asp Ile Ala Ile Asp Asp
 625 630 635

Val Lys Phe Gln Ala Gly Pro Cys Gly Glu Met Glu Asp Thr Thr Gln
 640 645 650

Gln Ser Ser Gly Tyr Ser Glu Asp Leu Asn Glu Ile Glu Tyr
 655 660 665

<210> 23

<211> 1581

<212> DNA

<213> Homo sapiens

<220>

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<222> (136)..(1386)

<220>

<221> mat_peptide

<222> (196)..()

<400> 23

ctcaattctt aaaaaataag tccatgaagc agaaaacatca.aaaagcatgg gatttggaat 60

ttgagacctg actttgaagc ccacacagaa cacagacaag tcaaccatgc tatttggac 120

atattttgtt ccaaa atg gca tct tac ctt tat gga gta ctc ttt gct gtt 171
 Met Ala Ser Tyr Leu Tyr Gly Val Leu Phe Ala Val
 -20 -15 -10

ggc ctc tgt gct cca atc tac tgt gtg tcc ccg gtc aat gcc ccc agt 219
 Gly Leu Cys Ala Pro Ile Tyr Cys Val Ser Pro Val Asn Ala Pro Ser
 -5 -1 1 5

gca tac ccc cgc cct tcc aca aag agc acc cct gcc tca cag gtg 267
 Ala Tyr Pro Arg Pro Ser Ser Thr Lys Ser Thr Pro Ala Ser Gln Val
 10 15 20

tat tcc ctc aac acc gac ttt gcc ttc cgc cta tac cgc agg ctg gtt 315
 Tyr Ser Leu Asn Thr Asp Phe Ala Phe Arg Leu Tyr Arg Arg Leu Val
 25 30 35 40

| | |
|---|-----|
| ttg gag acc ccg agt cag aac atc ttc ttc tcc cct gtg agt gtc tcc Leu Glu Thr Pro Ser Gln Asn Ile Phe Phe Ser Pro Val Ser Val Ser 45 50 55 | 363 |
| act tcc ctg gcc atg ctc tcc ctt ggg gcc cac tca gtc acc aag acc Thr Ser Leu Ala Met Leu Ser Leu Gly Ala His Ser Val Thr Lys Thr 60 65 70 | 411 |
| cag att ctc cag ggc ctg ggc ttc aac ctc aca cac aca cca gag tct Gln Ile Leu Gln Gly Leu Gly Phe Asn Leu Thr His Thr Pro Glu Ser 75 80 85 | 459 |
| gcc atc cac cag ggc ttc cag cac ctg gtt cac tca ctg act gtt ccc Ala Ile His Gln Gly Phe Gln His Leu Val His Ser Leu Thr Val Pro 90 95 100 | 507 |
| agc aaa gac ctg acc ttg aag atg gga agt gcc ctc ttc gtc aag aag Ser Lys Asp Leu Thr Leu Lys Met Gly Ser Ala Leu Phe Val Lys Lys 105 110 115 120 | 555 |
| gag ctg cag ctg cag gca aat ttc ttg ggc aat gtc aag agg ctg tat Glu Leu Gln Leu Gln Ala Asn Phe Leu Gly Asn Val Lys Arg Leu Tyr 125 130 135 | 603 |
| gaa gca gaa gtc ttt tct aca gat ttc tcc aac ccc tcc att gcc cag Glu Ala Glu Val Phe Ser Thr Asp Phe Ser Asn Pro Ser Ile Ala Gln 140 145 150 | 651 |
| gcg agg atc aac agc cat gtg aaa aag aag acc caa ggg aag gtt gta Ala Arg Ile Asn Ser His Val Lys Lys Thr Gln Gly Lys Val Val 155 160 165 | 699 |
| gac ata atc caa ggc ctt gac ctt ctg acg gcc atg gtt ctg gtg aat Asp Ile Ile Gln Gly Leu Asp Leu Leu Thr Ala Met Val Leu Val Asn 170 175 180 | 747 |
| cac att ttc ttt aaa gcc aag tgg gag aag ccc ttt cac ctt gaa tat His Ile Phe Phe Lys Ala Lys Trp Glu Lys Pro Phe His Leu Glu Tyr 185 190 195 200 | 795 |
| aca aga aag aac ttc cca ttc ctg gtg ggc gag cag gtc act gtg caa Thr Arg Lys Asn Phe Pro Phe Leu Val Gly Glu Gln Val Thr Val Gln 205 210 215 | 843 |
| gtc ccc atg atg cac cag aaa gag cag ttc gct ttt ggg gtg gat aca Val Pro Met Met His Gln Lys Glu Gln Phe Ala Phe Gly Val Asp Thr 220 225 230 | 891 |
| gag ctg aac tgc ttt gtg ctg cag atg gat tac aag gga gat gcc gtg Glu Leu Asn Cys Phe Val Leu Gln Met Asp Tyr Lys Gly Asp Ala Val 235 240 245 | 939 |

| | |
|---|------|
| gcc ttc ttt gtc ctc cct agc aag ggc aag atg agg caa ctg gaa cag Ala Phe Phe Val Leu Pro Ser Lys Gly Lys Met Arg Gln Leu Glu Gln 250 255 260 | 987 |
| gcc ttg tca gcc aga aca ctg ata aag tgg agc cac tca ctc cag aaa Ala Leu Ser Ala Arg Thr Leu Ile Lys Trp Ser His Ser Leu Gln Lys 265 270 275 280 | 1035 |
| agg tgg ata gag gtg ttc atc ccc aga ttt tcc att tct gcc tcc tac Arg Trp Ile Glu Val Phe Ile Pro Arg Phe Ser Ile Ser Ala Ser Tyr 285 290 295 | 1083 |
| aat ctg gaa acc atc ctc ccg aag atg ggc atc caa aat gcc ttt gac Asn Leu Glu Thr Ile Leu Pro Lys Met Gly Ile Gln Asn Ala Phe Asp 300 305 310 | 1131 |
| aaa aat gct gat ttt tct gca att gca aag aga gac tcc ctg cag gtt Lys Asn Ala Asp Phe Ser Gly Ile Ala Lys Arg Asp Ser Leu Gln Val 315 320 325 | 1179 |
| tct aaa gca acc cac aag gct gtg ctg gat gtc agt gaa gag ggc act Ser Lys Ala Thr His Lys Ala Val Leu Asp Val Ser Glu Glu Gly Thr 330 335 340 | 1227 |
| gag gcc aca gca gct acc acc acc aag ttc ata gtc cga tcg aag gat Glu Ala Thr Ala Ala Thr Thr Lys Phe Ile Val Arg Ser Lys Asp 345 350 355 360 | 1275 |
| ggt ccc tct tac ttc act gtc tcc ttc aat agg acc ttc ctg atg atg Gly Pro Ser Tyr Phe Thr Val Ser Phe Asn Arg Thr Phe Leu Met Met 365 370 375 | 1323 |
| att aca aat aaa gcc aca gac ggt att ctc ttt cta ggg aaa gtg gaa Ile Thr Asn Lys Ala Thr Asp Gly Ile Leu Phe Leu Gly Lys Val Glu 380 385 390 | 1371 |
| aat ccc act aaa tcc taggtggaa atggcctgtt aactgatggc acattgctaa Asn Pro Thr Lys Ser 395 | 1426 |
| tgcacaagaa ataacaaacc acatcccttt tctgttctga ggggcattt gaccccgatg ggagctggat tcgctggcag ggatgccacc ttccaggct caatcaccaa accatcaaca | 1486 |
| gggaccccgat tcacaagccaa acacccattt acccc | 1546 |
| 1581 | |

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-1 1 5 10

Pro Ser Ser Thr Lys Ser Thr Pro Ala Ser Gln Val Tyr Ser Leu Asn
15 20 25

Thr Asp Phe Ala Phe Arg Leu Tyr Arg Arg Leu Val Leu Glu Thr Pro
30 35 40

Ser Gln Asn Ile Phe Phe Ser Pro Val Ser Val Ser Thr Ser Leu Ala
45 50 55 60

Met Leu Ser Leu Gly Ala His Ser Val Thr Lys Thr Gln Ile Leu Gln
65 70 75

Gly Leu Gly Phe Asn Leu Thr His Thr Pro Glu Ser Ala Ile His Gln
80 85 90

Gly Phe Gln His Leu Val His Ser Leu Thr Val Pro Ser Lys Asp Leu
95 100 105

Thr Leu Lys Met Gly Ser Ala Leu Phe Val Lys Lys Glu Leu Gln Leu
110 115 120

Gln Ala Asn Phe Leu Gly Asn Val Lys Arg Leu Tyr Glu Ala Glu Val
125 130 135 140

Phe Ser Thr Asp Phe Ser Asn Pro Ser Ile Ala Gln Ala Arg Ile Asn
145 150 155

Ser His Val Lys Lys Lys Thr Gln Gly Lys Val Val Asp Ile Ile Gln
160 165 170

Gly Leu Asp Leu Leu Thr Ala Met Val Leu Val Asn His Ile Phe Phe
175 180 185

Lys Ala Lys Trp Glu Lys Pro Phe His Leu Glu Tyr Thr Arg Lys Asn
190 195 200

Phe Pro Phe Leu Val Gly Glu Gln Val Thr Val Gln Val Pro Met Met
205 210 215 220

His Gln Lys Glu Gln Phe Ala Phe Gly Val Asp Thr Glu Leu Asn Cys
225 230 235

Phe Val Leu Gln Met Asp Tyr Lys Gly Asp Ala Val Ala Phe Phe Val
240 245 250

Leu Pro Ser Lys Gly Lys Met Arg Gln Leu Glu Gln Ala Leu Ser Ala
255 260 265

Arg Thr Leu Ile Lys Trp Ser His Ser Leu Gln Lys Arg Trp Ile Glu
270 275 280

Val Phe Ile Pro Arg Phe Ser Ile Ser Ala Ser Tyr Asn Leu Glu Thr
285 290 295 300

Ile Leu Pro Lys Met Gly Ile Gln Asn Ala Phe Asp Lys Asn Ala Asp
305 310 315

Phe Ser Gly Ile Ala Lys Arg Asp Ser Leu Gln Val Ser Lys Ala Thr
320 325 330

His Lys Ala Val Leu Asp Val Ser Glu Glu Gly Thr Glu Ala Thr Ala
335 340 345

Ala Thr Thr Thr Lys Phe Ile Val Arg Ser Lys Asp Gly Pro Ser Tyr
350 355 360

Phe Thr Val Ser Phe Asn Arg Thr Phe Leu Met Met Ile Thr Asn Lys
365 370 375 380

Ala Thr Asp Gly Ile Leu Phe Leu Gly Lys Val Glu Asn Pro Thr Lys
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Ser

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 tgaacattga gg atg gcg cgt gcc cgc ggc tcc ccg tgc ccc ccg ctg ccg 171
 Met Ala Arg Ala Arg Gly Ser Pro Cys Pro Pro Leu Pro
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ccc ggt agg atg tcc tgg ccc cac ggg gca ttg ctc ttc ctc tgg ctc 219
 Pro Gly Arg Met Ser Trp Pro His Gly Ala Leu Leu Phe Leu Trp Leu
 -20 -15 -10

ttc tcc cca ccc ctg ggg gcc ggt gga ggt gga gtg gcc gtg acg tct 267
 Phe Ser Pro Pro Leu Gly Ala Gly Gly Gly Val Ala Val Thr Ser
 -5 -1 1 5

gcc gcc gga ggg ggc tcc ccg ccg gcc acc tcc tgc ccc gtg gcc tgc 315
 Ala Ala Gly Gly Ser Pro Pro Ala Thr Ser Cys Pro Val Ala Cys
 10 15 20 25

tcc tgc agc aac cag gcc agc cgg gtg atc tgc aca cgg aga gac ctg 363
 Ser Cys Ser Asn Gln Ala Ser Arg Val Ile Cys Thr Arg Arg Asp Leu
 30 35 40

gcc gag gtc cca gcc agc atc ccg gtc aac acg cgg tac ctg aac ctg 411
 Ala Glu Val Pro Ala Ser Ile Pro Val Asn Thr Arg Tyr Leu Asn Leu
 45 50 55

caa gag aac ggc atc cag gtg atc cgg acg gac acg ttc aag cac ctg 459
 Gln Glu Asn Gly Ile Gln Val Ile Arg Thr Asp Thr Phe Lys His Leu
 60 65 70

cgg cac ctg gag att ctg cag ctg agc aag aac ctg gtg cgc aag atc 507
 Arg His Leu Glu Ile Leu Gln Leu Ser Lys Asn Leu Val Arg Lys Ile
 75 80 85

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|---|------|
| gag gtg ggc gcc ttc aac ggg ctg ccc agc ctc aac acg ctg gag ctt | 555 |
| Glu Val Gly Ala Phe Asn Gly Leu Pro Ser Leu Asn Thr Leu Glu Leu | |
| 90 95 100 105 | |
| ttt gac aac cgg ctg acc acg gtg ccc acg cag gcc ttc gag tac ctg | 603 |
| Phe Asp Asn Arg Leu Thr Thr Val Pro Thr Gln Ala Phe Glu Tyr Leu | |
| 110 115 120 | |
| tcc aag ctg cgg gag ctc tgg ctg cgg aac aac ccc atc gag agc atc | 651 |
| Ser Lys Leu Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu Ser Ile | |
| 125 130 135 | |
| ccc tcc tac gcc ttc aac cgc gtg ccc tcg ctg cgg cgc ctg gac ctg | 699 |
| Pro Ser Tyr Ala Phe Asn Arg Val Pro Ser Leu Arg Arg Leu Asp Leu | |
| 140 145 150 | |
| ggc gag ctc aag cgg ctg gaa tac atc tcg gag gcg gcc ttc gag ggg | 747 |
| Gly Glu Leu Lys Arg Leu Glu Tyr Ile Ser Glu Ala Ala Phe Glu Gly | |
| 155 160 165 | |
| ctg gtc aac ctg cgc tac ctc aac ctg ggc atg tgc aac ctc aag gac | 795 |
| Leu Val Asn Leu Arg Tyr Leu Asn Leu Gly Met Cys Asn Leu Lys Asp | |
| 170 175 180 185 | |
| atc ccc aac ctg acg gcc ctg gtg cgc ctg gag gag ctg gag ctg tcg | 843 |
| Ile Pro Asn Leu Thr Ala Leu Val Arg Leu Glu Glu Leu Glu Leu Ser | |
| 190 195 200 | |
| ggc aac cgg ctg gac ctg atc cgc ccc ggc tcc ttc cag ggt ctc acc | 891 |
| Gly Asn Arg Leu Asp Leu Ile Arg Pro Gly Ser Phe Gln Gly Leu Thr | |
| 205 210 215 | |
| agc ctg cgc aag ctg tgg ctc atg cac gcc cag gta gcc acc atc gag | 939 |
| Ser Leu Arg Lys Leu Trp Leu Met His Ala Gln Val Ala Thr Ile Glu | |
| 220 225 230 | |
| cgc aac gcc ttc gac gac ctc aag tcg ctg gag gag ctc aac ctg tcc | 987 |
| Arg Asn Ala Phe Asp Asp Leu Lys Ser Leu Glu Glu Leu Asn Leu Ser | |
| 235 240 245 | |
| cac aac aac ctg atg tcg ctg ccc cac gac ctc ttc acg ccc ctg cac | 1035 |
| His Asn Asn Leu Met Ser Leu Pro His Asp Leu Phe Thr Pro Leu His | |
| 250 255 260 265 | |
| cgc ctc gag cgc gtg cac ctc aac cac aac ccc tgg cat tgc aac tgc | 1083 |
| Arg Leu Glu Arg Val His Leu Asn His Asn Pro Trp His Cys Asn Cys | |
| 270 275 280 | |
| gac gtg ctc tgg ctg agc tgg tgg ctc aag gag acg gtg ccc agc aac | 1131 |
| Asp Val Leu Trp Leu Ser Trp Trp Leu Lys Glu Thr Val Pro Ser Asn | |
| 285 290 295 | |

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|---|------|
| acg acg tgc tgc gcc cgc tgt cat gcg ccc gcc ggc ctc aag ggg cgc | 1179 |
| Thr Thr Cys Cys Ala Arg Cys His Ala Pro Ala Gly Leu Lys Gly Arg | |
| 300 305 310 | |
| | |
| tac att ggg gag ctg gac cag tcg cat ttc acc tgc tat gcg ccc gtc | 1227 |
| Tyr Ile Gly Glu Leu Asp Gln Ser His Phe Thr Cys Tyr Ala Pro Val | |
| 315 320 325 | |
| | |
| atc gtg gag ccg ccc acg gac ctc aac gtc acc gag ggc atg gct gcc | 1275 |
| Ile Val Glu Pro Pro Thr Asp Leu Asn Val Thr Glu Gly Met Ala Ala | |
| 330 335 340 345 | |
| | |
| gag ctc aaa tgc cgc acg ggc acc tcc atg acc tcc gtc aac tgg ctg | 1323 |
| Glu Leu Lys Cys Arg Thr Gly Thr Ser Met Thr Ser Val Asn Trp Leu | |
| 350 355 360 | |
| | |
| acg ccc aac ggc acc ctc atg acc cac ggc tcc tac cgc gtg cgc atc | 1371 |
| Thr Pro Asn Gly Thr Leu Met Thr His Gly Ser Tyr Arg Val Arg Ile | |
| 365 370 375 | |
| | |
| tcc gtc ctg cat gac ggc acg ctt aac ttc acc aac gtc acc gtg cag | 1419 |
| Ser Val Leu His Asp Gly Thr Leu Asn Phe Thr Asn Val Thr Val Gln | |
| 380 385 390 | |
| | |
| gac acg ggc cag tac acg tgc atg gtg acg aac tca gcc ggc aac acc | 1467 |
| Asp Thr Gly Gln Tyr Thr Cys Met Val Thr Asn Ser Ala Gly Asn Thr | |
| 395 400 405 | |
| | |
| acc gcc tcg gcc acg ctc aac gtc tcg gcc gtg gac ccc gtg gcg gcc | 1515 |
| Thr Ala Ser Ala Thr Leu Asn Val Ser Ala Val Asp Pro Val Ala Ala | |
| 410 415 420 425 | |
| | |
| ggg ggc acc ggc agc ggc ggg ggc cct ggg ggc agt ggt ggt gtt | 1563 |
| Gly Gly Thr Gly Ser Gly Gly Pro Gly Gly Ser Gly Gly Val | |
| 430 435 440 | |
| | |
| gga ggg ggc agt ggc ggc tac acc tac ttc acc acg gtg acc gtg gag | 1611 |
| Gly Gly Gly Ser Gly Gly Tyr Thr Phe Thr Thr Val Thr Val Glu | |
| 445 450 455 | |
| | |
| acc ctg gag acg cag ccc gga gag gag gcc ctg cag ccg cgg ggg acg | 1659 |
| Thr Leu Glu Thr Gln Pro Gly Glu Glu Ala Leu Gln Pro Arg Gly Thr | |
| 460 465 470 | |
| | |
| gag aag gaa ccg cca ggg ccc acg aca gac ggt gtc tgg ggt ggg ggc | 1707 |
| Glu Lys Glu Pro Pro Gly Pro Thr Thr Asp Gly Val Trp Gly Gly Gly | |
| 475 480 485 | |
| | |
| cgg cct ggg gac gcg gcc ggc cct gcc tcg tct tct acc acg gca ccc | 1755 |
| Arg Pro Gly Asp Ala Ala Gly Pro Ala Ser Ser Ser Thr Thr Ala Pro | |
| 490 495 500 505 | |

| | |
|--|------|
| gcc ccg cgc tcc tcg cg ^g ccc ac ^g gag a ^g g ^c g ttc ac ^g gt ^g ccc at ^c | 1803 |
| Ala Pro Arg Ser Ser Arg Pro Thr Glu Lys Ala Phe Thr Val Pro Ile | |
| 510 515 520 | |
| ac ^g gat gt ^g ac ^g gag a ^g aac g ^c ctc a ^g g ^c ac ^g ct ^g g ^c g ^c at ^g a ^g | 1851 |
| Thr Asp Val Thr Glu Asn Ala Leu Lys Asp Leu Asp Asp Val Met Lys | |
| 525 530 535 | |
| ac ^c acc aaa at ^c at ^c at ^c g ^g c t ^g c t ^t c gt ^g g ^c at ^c ac ^g t ^t c at ^g g ^c | 1899 |
| Thr Thr Lys Ile Ile Ile Gly Cys Phe Val Ala Ile Thr Phe Met Ala | |
| 540 545 550 | |
| g ^c g t ^g at ^g ctc gt ^g g ^c t ^t c tac a ^g ct ^g cgc a ^g c ^a g c ^a g c ^a ctc | 1947 |
| Ala Val Met Leu Val Ala Phe Tyr Lys Leu Arg Lys Gln His Gln Leu | |
| 555 560 565 | |
| cac a ^a g c ^a c ^a c ^a g ^g ccc ac ^g cgc acc g ^t g g ^a g at ^c at ^c a ^a c g ^t g g ^a | 1995 |
| His Lys His His Gly Pro Thr Arg Thr Val Glu Ile Ile Asn Val Glu | |
| 570 575 580 585 | |
| g ^a c g ^a ct ^g ccc g ^c g ^c t ^c g ^c t ^t c gt ^g g ^c g ^c g ^c g ^c g ^c | 2043 |
| Asp Glu Leu Pro Ala Ala Ser Ala Val Ser Val Ala Ala Ala Ala | |
| 590 595 600 | |
| gt ^g g ^c a ^g t g ^g g ^g t g ^g t g ^c g ^g g ^c a ^g c a ^g c c ^a c ct ^g g ^c ct ^g ccc | 2091 |
| Val Ala Ser Gly Gly Val Gly Gly Asp Ser His Leu Ala Leu Pro | |
| 605 610 615 | |
| g ^c c ^t g g ^a g c ^g a ^c c ^a c ^c t ^t c a ^a c ^a c ^a c ^a t ^a c gt ^g g ^c g ^c | 2139 |
| Ala Leu Glu Arg Asp His Leu Asn His His His Tyr Val Ala Ala Ala | |
| 620 625 630 | |
| t ^t c a ^a g g ^c c ^a t ^a c a ^g c a ^a c ^c a ^g c g ^g c g ^g c t ^g c g ^g g ^c | 2187 |
| Phe Lys Ala His Tyr Ser Ser Asn Pro Ser Gly Gly Cys Gly Gly | |
| 635 640 645 | |
| aaa g ^g c c ^g c ^c g ^g c t ^t c a ^a c ^t g at ^c c ^a c g ^a a c ^c t ct ^g c ^t c t ^t c a ^a g | 2235 |
| Lys Gly Pro Pro Gly Leu Asn Ser Ile His Glu Pro Leu Leu Phe Lys | |
| 650 655 660 665 | |
| ag ^c g ^g c t ^c c a ^a g g ^a a ^a c g ^t g c ^a a g ^a g ^c at ^c tgaggcggcg | 2281 |
| Ser Gly Ser Lys Glu Asn Val Gln Glu Thr Gln Ile | |
| 670 675 | |
| ggggccgggcg ggcgaggggc gtggagcccc ccacccaggt cccagcccc ggccagccctg | 2341 |
| accgggaccc ctccctccca cagccccagcc caccttctgg gaccacgcag ggaattgggg | 2401 |
| agaggtggct tccagcccca tctggggctc ggaccccccag taaggacagg gtggggctcc | 2461 |
| aggagcggag tctctggat cctcgctca ccccccggccaa tccccgggtga cggggagggga | 2521 |
| cgtgggaccc aggagaagtg gcctgagttc tccgcgttcc ctccctcgctc tccccaccaag | 2581 |

cgttccgggc ccggccgc tt ccagggaga gaggagctt ctccaggggt gtcctttacc 2641
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 gcgcccggtct ctgctcccg ccggcggtcc ctgtcgtcgg cgcggggggg agcctccacc 2821
 cgccccagcc ccacctgccc cacagacact tttgatactg aagggagggt tgcgtcaacg 2881
 actacctgct ctgtaattac tttaaaaaaa aaacatggaa aaagtaaaaaa aatattttt 2941
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 ggctggagag ccagcctcgc agctcc 3027

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<400> 26

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Met Ser Trp Pro His Gly Ala Leu Leu Phe Leu Trp Leu Phe Ser Pro
 -20 -15 -10 -5

Pro Leu Gly Ala Gly Gly Gly Val Ala Val Thr Ser Ala Ala Gly
 -1 1 5 10

Gly Gly Ser Pro Pro Ala Thr Ser Cys Pro Val Ala Cys Ser Cys Ser
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Asn Gln Ala Ser Arg Val Ile Cys Thr Arg Arg Asp Leu Ala Glu Val
 30 35 40

Pro Ala Ser Ile Pro Val Asn Thr Arg Tyr Leu Asn Leu Gln Glu Asn
 45 50 55 60

Gly Ile Gln Val Ile Arg Thr Asp Thr Phe Lys His Leu Arg His Leu
 65 70 75

Glu Ile Leu Gln Leu Ser Lys Asn Leu Val Arg Lys Ile Glu Val Gly
 80 85 90

Ala Phe Asn Gly Leu Pro Ser Leu Asn Thr Leu Glu Leu Phe Asp Asn
95 100 105

Arg Leu Thr Thr Val Pro Thr Gln Ala Phe Glu Tyr Leu Ser Lys Leu
110 115 120

Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu Ser Ile Pro Ser Tyr
125 130 135 140

Ala Phe Asn Arg Val Pro Ser Leu Arg Arg Leu Asp Leu Gly Glu Leu
145 150 155

Lys Arg Leu Glu Tyr Ile Ser Glu Ala Ala Phe Glu Gly Leu Val Asn
160 165 170

Leu Arg Tyr Leu Asn Leu Gly Met Cys Asn Leu Lys Asp Ile Pro Asn
175 180 185

Leu Thr Ala Leu Val Arg Leu Glu Glu Leu Glu Leu Ser Gly Asn Arg
190 195 200

Leu Asp Leu Ile Arg Pro Gly Ser Phe Gln Gly Leu Thr Ser Leu Arg
205 210 215 220

Lys Leu Trp Leu Met His Ala Gln Val Ala Thr Ile Glu Arg Asn Ala
225 230 235

Phe Asp Asp Leu Lys Ser Leu Glu Glu Leu Asn Leu Ser His Asn Asn
240 245 250

Leu Met Ser Leu Pro His Asp Leu Phe Thr Pro Leu His Arg Leu Glu
255 260 265

Arg Val His Leu Asn His Asn Pro Trp His Cys Asn Cys Asp Val Leu
270 275 280

Trp Leu Ser Trp Trp Leu Lys Glu Thr Val Pro Ser Asn Thr Thr Cys
285 290 295 300

Cys Ala Arg Cys His Ala Pro Ala Gly Leu Lys Gly Arg Tyr Ile Gly
305 310 315

Glu Leu Asp Gln Ser His Phe Thr Cys Tyr Ala Pro Val Ile Val Glu
320 325 330

Pro Pro Thr Asp Leu Asn Val Thr Glu Gly Met Ala Ala Glu Leu Lys
335 340 345

Cys Arg Thr Gly Thr Ser Met Thr Ser Val Asn Trp Leu Thr Pro Asn
350 355 360

Gly Thr Leu Met Thr His Gly Ser Tyr Arg Val Arg Ile Ser Val Leu
365 370 375 380

His Asp Gly Thr Leu Asn Phe Thr Asn Val Thr Val Gln Asp Thr Gly
385 390 395

Gln Tyr Thr Cys Met Val Thr Asn Ser Ala Gly Asn Thr Thr Ala Ser
400 405 410

Ala Thr Leu Asn Val Ser Ala Val Asp Pro Val Ala Ala Gly Thr
415 420 425

Gly Ser Gly Gly Gly Pro Gly Gly Ser Gly Gly Val Gly Gly Gly
430 435 440

Ser Gly Gly Tyr Thr Tyr Phe Thr Thr Val Thr Val Glu Thr Leu Glu
445 450 455 460

Thr Gln Pro Gly Glu Glu Ala Leu Gln Pro Arg Gly Thr Glu Lys Glu
465 470 475

Pro Pro Gly Pro Thr Thr Asp Gly Val Trp Gly Gly Arg Pro Gly
480 485 490

Asp Ala Ala Gly Pro Ala Ser Ser Ser Thr Thr Ala Pro Ala Pro Arg
495 500 505

Ser Ser Arg Pro Thr Glu Lys Ala Phe Thr Val Pro Ile Thr Asp Val
510 515 520

Thr Glu Asn Ala Leu Lys Asp Leu Asp Asp Val Met Lys Thr Thr Lys
525 530 535 540

Ile Ile Ile Gly Cys Phe Val Ala Ile Thr Phe Met Ala Ala Val Met
545 550 555

Leu Val Ala Phe Tyr Lys Leu Arg Lys Gln His Gln Leu His Lys His
560 565 570

His Gly Pro Thr Arg Thr Val Glu Ile Ile Asn Val Glu Asp Glu Leu
575 580 585

Pro Ala Ala Ser Ala Val Ser Val Ala Ala Ala Ala Val Ala Ser
590 595 600

Gly Gly Gly Val Gly Gly Asp Ser His Leu Ala Leu Pro Ala Leu Glu
605 610 615 620

Arg Asp His Leu Asn His His Tyr Val Ala Ala Ala Phe Lys Ala
625 630 635

His Tyr Ser Ser Asn Pro Ser Gly Gly Cys Gly Gly Lys Gly Pro
640 645 650

Pro Gly Leu Asn Ser Ile His Glu Pro Leu Leu Phe Lys Ser Gly Ser
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Lys Glu Asn Val Gln Glu Thr Gln Ile
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| tccattagga agtcctggtc agcagcttgg gcgag atg gca gag tca ggg ctg | | 113 |
| Met Ala Glu Ser Gly Leu | | |
| -25 | | -20 |
| gcc atg tgg ccg agc ctg ctg ctc ctg ctg ttg ccg ggg ccc ccg | | 161 |
| Ala Met Trp Pro Ser Leu Leu Leu Leu Leu Leu Pro Gly Pro Pro | | |
| -15 | | -5 |
| ccc gtc gcc ggc ttg gaa gac gct gcc ttc ccc cac ctg ggg gag agc | | 209 |
| Pro Val Ala Gly Leu Glu Asp Ala Ala Phe Pro His Leu Gly Glu Ser | | |
| -1 1 5 10 | | |
| ttg cag ccc ctg ccc cgg gcc tgg ccc ctg cgc tgc tcc tgc ccc cga | | 257 |
| Leu Gln Pro Leu Pro Arg Ala Cys Pro Leu Arg Cys Ser Cys Pro Arg | | |
| 15 20 25 | | |
| gtc gac act gtg gac tgg gat ggc ttg gac ctt cga gtg ttc ccg gac | | 305 |
| Val Asp Thr Val Asp Cys Asp Gly Leu Asp Leu Arg Val Phe Pro Asp | | |
| 30 35 40 45 | | |
| aac atc acc aga gcc gct cag cac ctc tcc ctg cag aac aac cag ctc | | 353 |
| Asn Ile Thr Arg Ala Ala Gln His Leu Ser Leu Gln Asn Asn Gln Leu | | |
| 50 55 60 | | |
| cag gaa ctc ccc tac aat gag ctg tcc cgc ctc agt ggc ctg cga acc | | 401 |
| Gln Glu Leu Pro Tyr Asn Glu Leu Ser Arg Leu Ser Gly Leu Arg Thr | | |
| 65 70 75 | | |
| ctc aac ctc cac aac aac ctc atc tcc tcc gaa ggc ctg cct gac gag | | 449 |
| Leu Asn Leu His Asn Asn Ile Ser Ser Glu Gly Leu Pro Asp Glu | | |
| 80 85 90 | | |
| gcc ttc gag tcc ctc acc cag ctg cag cac ctc tgc gtg gct cac aac | | 497 |
| Ala Phe Glu Ser Leu Thr Gln Leu Gln His Leu Cys Val Ala His Asn | | |
| 95 100 105 | | |
| aag aac aat ctc atc tcc aag gtg ccc cga gga gcc ctg agc cgc cag | | 545 |
| Lys Asn Asn Leu Ile Ser Lys Val Pro Arg Gly Ala Leu Ser Arg Gln | | |
| 110 115 120 125 | | |
| act caa ctc cgt gag ctc tac ctc cag cac aac cag ctg aca gac agt | | 593 |
| Thr Gln Leu Arg Glu Leu Tyr Leu Gln His Asn Gln Leu Thr Asp Ser | | |
| 130 135 140 | | |
| ggc ctg gat gcc acc acc ttc agc aag ctg cat agc ctt gaa tac ctg | | 641 |
| Gly Leu Asp Ala Thr Thr Phe Ser Lys Leu His Ser Leu Glu Tyr Leu | | |
| 145 150 155 | | |

| | |
|---|------|
| gat ctc tcc cac aac cag ctg acc aca gtg ccc gcc ggc ctg ccc cgg Asp Leu Ser His Asn Gln Leu Thr Thr Val Pro Ala Gly Leu Pro Arg 160 165 170 | 689 |
| acc ctg gct atc ctg cac ctg ggc cgc aac cgc atc cgg cag gtg gag Thr Leu Ala Ile Leu His Leu Gly Arg Asn Arg Ile Arg Gln Val Glu 175 180 185 | 737 |
| gcg gct cgg ctg cac ggg ggc cgt ggt ctg cgc tat ttg ttg ctg cag Ala Ala Arg Leu His Gly Ala Arg Gly Leu Arg Tyr Leu Leu Gln 190 195 200 205 | 785 |
| cac aac cag ctg ggg agc tca ggg ctg ccc gcc ggg gct ctg cgg ccg His Asn Gln Leu Gly Ser Ser Gly Leu Pro Ala Gly Ala Leu Arg Pro 210 215 220 | 833 |
| ctg cgg ggc ctg cac acg ctg cac ctc tat ggc aat ggg ctg gac cgc Leu Arg Gly Leu His Thr Leu His Leu Tyr Gly Asn Gly Leu Asp Arg 225 230 235 | 881 |
| gtg cct cca gcc ctg ccc cgc cgc ctg cgt gcc ctg gtg ctg ccc cac Val Pro Pro Ala Leu Pro Arg Arg Leu Arg Ala Leu Val Leu Pro His 240 245 250 | 929 |
| aac cac gtg gcc ggc ctg ggt gcc cgt gac ctg gtc gcc aca ccg ggc Asn His Val Ala Ala Leu Gly Ala Arg Asp Leu Val Ala Thr Pro Gly 255 260 265 | 977 |
| ctg acg gag ctt aac ctg gcc tat aac cgc ctg gcc agc gac cgt gtg Leu Thr Glu Leu Asn Leu Ala Tyr Asn Arg Leu Ala Ser Ala Arg Val 270 275 280 285 | 1025 |
| cac cac cgg gcc ttc cgc cgg ttg cgt gcc ctg cgc agc ctc gac ctg His His Arg Ala Phe Arg Arg Leu Arg Ala Leu Arg Ser Leu Asp Leu 290 295 300 | 1073 |
| gca ggg aat cag cta acc cgg ctg ccc atg ggc ctg ccc act ggc ctg Ala Gly Asn Gln Leu Thr Arg Leu Pro Met Gly Leu Pro Thr Gly Leu 305 310 315 | 1121 |
| cgc acc ctg cag ctg caa cgc aac cag ctg cgg atg ctc gag ccc gag Arg Thr Leu Gln Leu Gln Arg Asn Gln Leu Arg Met Leu Glu Pro Glu 320 325 330 | 1169 |
| cct ctg gcc ggc ctg gac caa ctg cgg gag ctc agc ctg gcg cac aac Pro Leu Ala Gly Leu Asp Gln Leu Arg Glu Leu Ser Leu Ala His Asn 335 340 345 | 1217 |
| cgg ctc cgg gtc ggc gac atc ggg cca ggc acc tgg cat gag ctc caa Arg Leu Arg Val Gly Asp Ile Gly Pro Gly Thr Trp His Glu Leu Gln 350 355 360 365 | 1265 |

gcc ctc cag gtc agg cac agg ctg gtt agc cac act gtc ccc agg gcc 1313
 Ala Leu Gln Val Arg His Arg Leu Val Ser His Thr Val Pro Arg Ala
 370 375 380

cct cca tcc ccc tgc ctg ccc tgc cac gtc cca aac att cta gtt agc 1361
 Pro Pro Ser Pro Cys Leu Pro Cys His Val Pro Asn Ile Leu Val Ser
 385 390 395

tgg taaagcaatc agaacaagaa aatgataaga gtgggttaga aggtgatgag ga 1416
 Trp

<210> 28
 <211> 423
 <212> PRT
 <213> Homo sapiens

<400> 28

Met Ala Glu Ser Gly Leu Ala Met Trp Pro Ser Leu Leu Leu Leu
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Leu Leu Pro Gly Pro Pro Pro Val Ala Gly Leu Glu Asp Ala Ala Phe
 -5 -1 1 5

Pro His Leu Gly Glu Ser Leu Gln Pro Leu Pro Arg Ala Cys Pro Leu
 10 15 20

Arg Cys Ser Cys Pro Arg Val Asp Thr Val Asp Cys Asp Gly Leu Asp
 25 30 35

Leu Arg Val Phe Pro Asp Asn Ile Thr Arg Ala Ala Gln His Leu Ser
 40 45 50 55

Leu Gln Asn Asn Gln Leu Gln Glu Leu Pro Tyr Asn Glu Leu Ser Arg
 60 65 70

Leu Ser Gly Leu Arg Thr Leu Asn Leu His Asn Asn Leu Ile Ser Ser
 75 80 85

Glu Gly Leu Pro Asp Glu Ala Phe Glu Ser Leu Thr Gln Leu Gln His
 90 95 100

Leu Cys Val Ala His Asn Lys Asn Asn Leu Ile Ser Lys Val Pro Arg
 105 110 115

Gly Ala Leu Ser Arg Gln Thr Gln Leu Arg Glu Leu Tyr Leu Gln His
120 125 130 135

Asn Gln Leu Thr Asp Ser Gly Leu Asp Ala Thr Thr Phe Ser Lys Leu
140 145 150

His Ser Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu Thr Thr Val
155 160 165

Pro Ala Gly Leu Pro Arg Thr Leu Ala Ile Leu His Leu Gly Arg Asn
170 175 180

Arg Ile Arg Gln Val Glu Ala Ala Arg Leu His Gly Ala Arg Gly Leu
185 190 195

Arg Tyr Leu Leu Leu Gln His Asn Gln Leu Gly Ser Ser Gly Leu Pro
200 205 210 215

Ala Gly Ala Leu Arg Pro Leu Arg Gly Leu His Thr Leu His Leu Tyr
220 225 230

Gly Asn Gly Leu Asp Arg Val Pro Pro Ala Leu Pro Arg Arg Leu Arg
235 240 245

Ala Leu Val Leu Pro His Asn His Val Ala Ala Leu Gly Ala Arg Asp
250 255 260

Leu Val Ala Thr Pro Gly Leu Thr Glu Leu Asn Leu Ala Tyr Asn Arg
265 270 275

Leu Ala Ser Ala Arg Val His His Arg Ala Phe Arg Arg Leu Arg Ala
280 285 290 295

Leu Arg Ser Leu Asp Leu Ala Gly Asn Gln Leu Thr Arg Leu Pro Met
300 305 310

Gly Leu Pro Thr Gly Leu Arg Thr Leu Gln Leu Gln Arg Asn Gln Leu
315 320 325

Arg Met Leu Glu Pro Glu Pro Leu Ala Gly Leu Asp Gln Leu Arg Glu
 330 335 340

Leu Ser Leu Ala His Asn Arg Leu Arg Val Gly Asp Ile Gly Pro Gly
 345 350 355

Thr Trp His Glu Leu Gln Ala Leu Gln Val Arg His Arg Leu Val Ser
 360 365 370 375

His Thr Val Pro Arg Ala Pro Pro Ser Pro Cys Leu Pro Cys His Val
 380 385 390

Pro Asn Ile Leu Val Ser Trp
 395

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 <222> (76) .. ()

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 Met Thr Pro Gln Leu Leu Ala Leu
 -15 -10

gtc ctc tgg gcc agc tgc ccg ccc tgc agt gga agg aaa ggg ccc cca 99
 Val Leu Trp Ala Ser Cys Pro Pro Cys Ser Gly Arg Lys Gly Pro Pro
 -5 -1 1 5

gca gct ctg aca ctg ccc ccg gtg caa tgc cga gcc tct cgg tac ccg 147
 Ala Ala Leu Thr Leu Pro Arg Val Gln Cys Arg Ala Ser Arg Tyr Pro
 10 15 20

atc gcc gtg gat tgc tcc tgg acc ctg ccg cct gct cca aac tcc acc 195
 Ile Ala Val Asp Cys Ser Trp Thr Leu Pro Pro Ala Pro Asn Ser Thr
 25 30 35 40

agc ccc gtg tcc ttc att gcc acg tac agg tcg gag agc ctg gaa ggg 243
 Ser Pro Val Ser Phe Ile Ala Thr Tyr Arg Ser Glu Ser Leu Glu Gly
 45 50 55

ggc ctc agg gac act gga ctt cct gga gag ccc aga act ctg gcc ctg 291
Gly Leu Arg Asp Thr Gly Leu Pro Gly Glu Pro Arg Thr Leu Ala Leu
60 65 70

aga gcc ctg ggg tca gga aaa ctg gag acc ccg aca tcc tgaaccccag 340
Arg Ala Leu Gly Ser Gly Lys Leu Glu Thr Pro Thr Ser
75 80 85

gcctatggaa ttcttagggcg gccccgtcca atagaaatat actttctggg ccagggaaaaaa 400
aaaaaaaaaaaa aaaaaaaaaa aaaaaaaaaa gaaaaaaaaa aaaaa 445

<210> 30
<211> 102
<212> PRT
<213> Homo sapiens

<400> 30

Met Thr Pro Gln Leu Leu Leu Ala Leu Val Leu Trp Ala Ser Cys Pro
-15 -10 -5

Pro Cys Ser Gly Arg Lys Gly Pro Pro Ala Ala Leu Thr Leu Pro Arg
-1 1 5 10 15

Val Gln Cys Arg Ala Ser Arg Tyr Pro Ile Ala Val Asp Cys Ser Trp
20 25 30

Thr Leu Pro Pro Ala Pro Asn Ser Thr Ser Pro Val Ser Phe Ile Ala
35 40 45

Thr Tyr Arg Ser Glu Ser Leu Glu Gly Leu Arg Asp Thr Gly Leu
50 55 60

Pro Gly Glu Pro Arg Thr Leu Ala Leu Arg Ala Leu Gly Ser Gly Lys
65 70 75

Leu Glu Thr Pro Thr Ser
80 85

<210> 31
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<213> Homo sapiens

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<400> 31 48
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 Met Val Ser Pro Arg Met Ser Gly Leu Leu Ser Gln Thr Val Ile Leu
 -25 -20 -15

gcg ctc att ttc ctc ccc cag aca cgg ccc gct ggc gtc ttc gag ctg 96
 Ala Leu Ile Phe Leu Pro Gln Thr Arg Pro Ala Gly Val Phe Glu Leu
 -10 -5 -1 1 5

cag atc cac tct ttc ggg ccg ggt cca ggc cct ggg gcc ccg cgg tcc 144
 Gln Ile His Ser Phe Gly Pro Gly Pro Gly Ala Pro Arg Ser
 10 15 20

ccc tgc agc gcc cgg ctc ccc tgc cgc ctc ttc ttc aga gtc tgc ctg 192
 Pro Cys Ser Ala Arg Leu Pro Cys Arg Leu Phe Phe Arg Val Cys Leu
 25 30 35

aag cct ggg ctc tca gag gag gcc gag tcc ccg tgc gcc ctg ggc 240
 Lys Pro Gly Leu Ser Glu Glu Ala Ala Glu Ser Pro Cys Ala Leu Gly
 40 45 50

gcg gcg ctg agt gcg cgc gga ccg gtc tac acc gag cag ccc gga gcg 288
 Ala Ala Leu Ser Ala Arg Gly Pro Val Tyr Thr Glu Gln Pro Gly Ala
 55 60 65 70

ccc gcg cct gat ctc cca ctg ccc gac ggc ctc ttg cag gtg ccc ttc 336
 Pro Ala Pro Asp Leu Pro Leu Pro Asp Gly Leu Leu Gln Val Pro Phe
 75 80 85

cgg gac gcc tgg cct ggc acc ttc tct ttc atc atc gaa acc acc tgg aga 384
 Arg Asp Ala Trp Pro Gly Thr Phe Ser Phe Ile Ile Glu Thr Trp Arg
 90 95 100

gag gag tta gga gac cag att gga ggg ccc gcc tgg agc ctg ctg gcg 432
 Glu Glu Leu Gly Asp Gln Ile Gly Gly Pro Ala Trp Ser Leu Leu Ala
 105 110 115

cgc gtg gct ggc agg cgg cgc ttg gca gcc gga ggc ccg tgg gcc cgg 480
 Arg Val Ala Gly Arg Arg Leu Ala Ala Gly Gly Pro Trp Ala Arg

120 125 130

gac att cag cgc gca ggc gcc tgg gag ctg cgc tgc tcg tac cgc gcg 528
 Asp Ile Gln Arg Ala Gly Ala Trp Glu Leu Arg Cys Ser Tyr Arg Ala
 135 140 145 150

| | | | | |
|---|-----|-----|------|------|
| ccg tgc gag ccg cct gcg gtc ggg acc gcg tgc acg cgc ctc tgc cgt Arg Cys Glu Pro Pro Ala Val Gly Thr Ala Cys Thr Arg Leu Cys Arg 155 | 160 | 165 | 576 | |
| ccg ccg agc gcc ccc tcg cgg tgc ggt ccg gga ctg cgc ccc tgc gca Pro Arg Ser Ala Pro Ser Arg Cys Gly Pro Gly Leu Arg Pro Cys Ala 170 | 175 | 180 | 624 | |
| ccg ctc gag gac gaa tgt gag gcg ccg gtg tgc cga gca ggc tgc Pro Leu Glu Asp Glu Cys Ala Pro Pro Val Cys Arg Ala Gly Cys 185 | 190 | 195 | 672 | |
| agc cct gag cat ggc ttc tgt gaa cag ccc ggt gaa tgc cga tgc cta Ser Pro Glu His Gly Phe Cys Glu Gln Pro Gly Glu Cys Arg Cys Leu 200 | 205 | 210 | 720 | |
| gag ggc tgg act gga ccc ctc tgc acg gtc cct gtc tcc acc agc agc Glu Gly Trp Thr Gly Pro Leu Cys Thr Val Pro Val Ser Thr Ser Ser 215 | 220 | 225 | 230 | 768 |
| tgc ctc agc ccc agg ggc ccg tcc tct gct acc acc gga tgc ctt gtc Cys Leu Ser Pro Arg Gly Pro Ser Ser Ala Thr Thr Gly Cys Leu Val 235 | 240 | 245 | 816 | |
| cct ggg cct ggg ccc tgt gac ggg aac ccg tgt gcc aat gga ggc agc Pro Gly Pro Gly Pro Cys Asp Gly Asn Pro Cys Ala Asn Gly Gly Ser 250 | 255 | 260 | 864 | |
| tgt agt gag aca ccc agg tcc ttt gaa tgc acc tgc ccg cgt ggg ttc Cys Ser Glu Thr Pro Arg Ser Phe Glu Cys Thr Cys Pro Arg Gly Phe 265 | 270 | 275 | 912 | |
| tac ggg ctg cgg tgt gag gtg agc ggg gtg aca tgt gca gat gga ccc Tyr Gly Leu Arg Cys Glu Val Ser Gly Val Thr Cys Ala Asp Gly Pro 280 | 285 | 290 | 960 | |
| tgc ttc aac ggc ggc ttg tgt gtc ggg ggt gca gac cct gac tct gcc Cys Phe Asn Gly Gly Leu Cys Val Gly Gly Ala Asp Pro Asp Ser Ala 295 | 300 | 305 | 310 | 1008 |
| tac atc tgc cac tgc cca cct ggt ttc caa ggc tcc aac tgt gag aag Tyr Ile Cys His Cys Pro Pro Gly Phe Gln Gly Ser Asn Cys Glu Lys 315 | 320 | 325 | 1056 | |
| agg gtg gac cgg tgc agc ctg cag cca tgc cgc aat ggc gga ctc tgc Arg Val Asp Arg Cys Ser Leu Gln Pro Cys Arg Asn Gly Gly Leu Cys 330 | 335 | 340 | 1104 | |
| ctg gac ctg ggc cac gcc ctg cgc tgc cgc tgc cgc gcc ggc ttc gcg Leu Asp Leu Gly His Ala Leu Arg Cys Arg Cys Arg Ala Gly Phe Ala 345 | 350 | 355 | 1152 | |

| | |
|---|------|
| ggt cct cgc tgc gag cac gac ctg gac gac tgc gcg ggc cgc gcc tgc | 1200 |
| Gly Pro Arg Cys Glu His Asp Leu Asp Asp Cys Ala Gly Arg Ala Cys | |
| 360 365 370 | |
| gct aac ggc ggc acg tgt gtg gag ggc ggc ggc gcg cac cgc tgc tcc | 1248 |
| Ala Asn Gly Gly Thr Cys Val Glu Gly Gly Ala His Arg Cys Ser | |
| 375 380 385 390 | |
| tgc gcg ctg ggc ttc ggc ggc cgc gac tgc cgc gag cgc gcg gac ccg | 1296 |
| Cys Ala Leu Gly Phe Gly Gly Arg Asp Cys Arg Glu Arg Ala Asp Pro | |
| 395 400 405 | |
| tgc gcc gcg cgc ccc tgt gct cac ggc ggc cgc tgc tac gcc cac ttc | 1344 |
| Cys Ala Ala Arg Pro Cys Ala His Gly Gly Arg Cys Tyr Ala His Phe | |
| 410 415 420 | |
| tcc ggc ctc gtc tgc gct tgc gct ccc ggc tac atg gga gcg cgg tgt | 1392 |
| Ser Gly Leu Val Cys Ala Cys Ala Pro Gly Tyr Met Gly Ala Arg Cys | |
| 425 430 435 | |
| gag ttc cca gtg cac ccc gac ggc gca agc gcc ttg ccc gcg gcc ccg | 1440 |
| Glu Phe Pro Val His Pro Asp Gly Ala Ser Ala Leu Pro Ala Ala Pro | |
| 440 445 450 | |
| ccg ggc ctc agg ccc ggg gac cct cag cgc tac ctt ttg cct ccg gct | 1488 |
| Pro Gly Leu Arg Pro Gly Asp Pro Gln Arg Tyr Leu Leu Pro Pro Ala | |
| 455 460 465 470 | |
| ctg gga ctg ctc gtg gcc ggc gtg gcc ggc gct gcg ctc ttg ctg | 1536 |
| Leu Gly Leu Leu Val Ala Ala Gly Val Ala Gly Ala Leu Leu Leu | |
| 475 480 485 | |
| gtc cac gtg cgc cgc cgt ggc cac tcc cag gat gct ggg tct cgc ttg | 1584 |
| Val His Val Arg Arg Gly His Ser Gln Asp Ala Gly Ser Arg Leu | |
| 490 495 500 | |
| ctg gct ggg acc ccg gag ccg tca gtc cac gca ctc ccg gat gca ctc | 1632 |
| Leu Ala Gly Thr Pro Glu Pro Ser Val His Ala Leu Pro Asp Ala Leu | |
| 505 510 515 | |
| aac aac cta agg acg cag gag ggt tcc ggg gat ggt ccg agc tcg tcc | 1680 |
| Asn Asn Leu Arg Thr Gln Glu Gly Ser Gly Asp Gly Pro Ser Ser Ser | |
| 520 525 530 | |
| gta gat tgg aat cgc cct gaa gat gta gac cct caa ggg att tat gtc | 1728 |
| Val Asp Trp Asn Arg Pro Glu Asp Val Asp Pro Gln Gly Ile Tyr Val | |
| 535 540 545 550 | |
| ata tct gct cct tcc atc tac gct cgg gag gcc tgacgcgtct cctccatccg | 1781 |
| Ile Ser Ala Pro Ser Ile Tyr Ala Arg Glu Ala | |
| 555 560 | |
| cacctggagt cagagcgtgg atttttgtat ttgctcggtg gtgcccccagtc tctgccccag | 1841 |

aggctttgga gttcaat

1858

<210> 32
<211> 587
<212> PRT
<213> Homo sapiens

<400> 32

Met Val Ser Pro Arg Met Ser Gly Leu Leu Ser Gln Thr Val Ile Leu
-25 -20 -15

Ala Leu Ile Phe Leu Pro Gln Thr Arg Pro Ala Gly Val Phe Glu Leu
-10 -5 -1 1 5

Gln Ile His Ser Phe Gly Pro Gly Pro Gly Ala Pro Arg Ser
10 15 20

Pro Cys Ser Ala Arg Leu Pro Cys Arg Leu Phe Phe Arg Val Cys Leu
25 30 35

Lys Pro Gly Leu Ser Glu Glu Ala Ala Glu Ser Pro Cys Ala Leu Gly
40 45 50

Ala Ala Leu Ser Ala Arg Gly Pro Val Tyr Thr Glu Gln Pro Gly Ala
55 60 65 70

Pro Ala Pro Asp Leu Pro Leu Pro Asp Gly Leu Leu Gln Val Pro Phe
75 80 85

Arg Asp Ala Trp Pro Gly Thr Phe Ser Phe Ile Ile Glu Thr Trp Arg
90 95 100

Glu Glu Leu Gly Asp Gln Ile Gly Gly Pro Ala Trp Ser Leu Leu Ala
105 110 115

Arg Val Ala Gly Arg Arg Arg Leu Ala Ala Gly Gly Pro Trp Ala Arg
120 125 130

Asp Ile Gln Arg Ala Gly Ala Trp Glu Leu Arg Cys Ser Tyr Arg Ala
135 140 145 150

Arg Cys Glu Pro Pro Ala Val Gly Thr Ala Cys Thr Arg Leu Cys Arg
155 160 165

Pro Arg Ser Ala Pro Ser Arg Cys Gly Pro Gly Leu Arg Pro Cys Ala
170 175 180

Pro Leu Glu Asp Glu Cys Glu Ala Pro Pro Val Cys Arg Ala Gly Cys
185 190 195

Ser Pro Glu His Gly Phe Cys Glu Gln Pro Gly Glu Cys Arg Cys Leu
200 205 210

Glu Gly Trp Thr Gly Pro Leu Cys Thr Val Pro Val Ser Thr Ser Ser
215 220 225 230

Cys Leu Ser Pro Arg Gly Pro Ser Ser Ala Thr Thr Gly Cys Leu Val
235 240 245

Pro Gly Pro Gly Pro Cys Asp Gly Asn Pro Cys Ala Asn Gly Gly Ser
250 255 260

Cys Ser Glu Thr Pro Arg Ser Phe Glu Cys Thr Cys Pro Arg Gly Phe
265 270 275

Tyr Gly Leu Arg Cys Glu Val Ser Gly Val Thr Cys Ala Asp Gly Pro
280 285 290

Cys Phe Asn Gly Gly Leu Cys Val Gly Ala Asp Pro Asp Ser Ala
295 300 305 310

Tyr Ile Cys His Cys Pro Pro Gly Phe Gln Gly Ser Asn Cys Glu Lys
315 320 325

Arg Val Asp Arg Cys Ser Leu Gln Pro Cys Arg Asn Gly Gly Leu Cys
330 335 340

Leu Asp Leu Gly His Ala Leu Arg Cys Arg Cys Arg Ala Gly Phe Ala
345 350 355

Gly Pro Arg Cys Glu His Asp Leu Asp Asp Cys Ala Gly Arg Ala Cys
360 365 370

Ala Asn Gly Gly Thr Cys Val Glu Gly Gly Ala His Arg Cys Ser
375 380 385 390

Cys Ala Leu Gly Phe Gly Gly Arg Asp Cys Arg Glu Arg Ala Asp Pro
395 400 405

Cys Ala Ala Arg Pro Cys Ala His Gly Gly Arg Cys Tyr Ala His Phe
410 415 420

Ser Gly Leu Val Cys Ala Cys Ala Pro Gly Tyr Met Gly Ala Arg Cys
425 430 435

Glu Phe Pro Val His Pro Asp Gly Ala Ser Ala Leu Pro Ala Ala Pro
440 445 450

Pro Gly Leu Arg Pro Gly Asp Pro Gln Arg Tyr Leu Leu Pro Pro Ala
455 460 465 470

Leu Gly Leu Leu Val Ala Ala Gly Val Ala Gly Ala Ala Leu Leu Leu
475 480 485

Val His Val Arg Arg Gly His Ser Gln Asp Ala Gly Ser Arg Leu
490 495 500

Leu Ala Gly Thr Pro Glu Pro Ser Val His Ala Leu Pro Asp Ala Leu
505 510 515

Asn Asn Leu Arg Thr Gln Glu Gly Ser Gly Asp Gly Pro Ser Ser Ser
520 525 530

Val Asp Trp Asn Arg Pro Glu Asp Val Asp Pro Gln Gly Ile Tyr Val
535 540 545 550

Ile Ser Ala Pro Ser Ile Tyr Ala Arg Glu Ala
555 560

<210> 33
 <211> 1968
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 Met Gly Thr Val Ser Ser Arg Arg Ser
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 Trp Trp Pro Leu Pro Leu Leu Leu Leu Leu Leu Leu Leu Gly Pro
 -5 -1 1 5

 gcg ggc gcc cgt gcg cag gag gac gac ggc gac tac gag gag ctg 147
 Ala Gly Ala Arg Ala Gln Glu Asp Glu Asp Gly Asp Tyr Glu Glu Leu
 10 15 20

 gtg cta gcc ttg cgt tcc gag gag gac ggc ctg gcc gaa gca ccc gag 195
 Val Leu Ala Leu Arg Ser Glu Glu Asp Gly Leu Ala Glu Ala Pro Glu
 25 30 35

 cac gga acc aca gcc acc ttc cac cgc tgc gcc aag gat ccg tgg agg 243
 His Gly Thr Thr Ala Thr Phe His Arg Cys Ala Lys Asp Pro Trp Arg
 40 45 50 55

 ttg cct ggc acc tac gtg gtg ctg aag gag gag acc cac ctc tcc 291
 Leu Pro Gly Thr Tyr Val Val Leu Lys Glu Glu Thr His Leu Ser
 60 65 70

 cag tca gag cgc act gcc cgc cgc ctg cag gcc cag gct gcc cgc cgg 339
 Gln Ser Glu Arg Thr Ala Arg Arg Leu Gln Ala Gln Ala Ala Arg Arg
 75 80 85

 gga tac ctc acc aag atc ctg cat gtc ttc cat ggc ctt ctt cct ggc 387
 Gly Tyr Leu Thr Lys Ile Leu His Val Phe His Gly Leu Leu Pro Gly
 90 95 100

 ttc ctg gtg aag atg agt ggc gac ctg ctg gag ctg gcc ttg aag ttg 435
 Phe Leu Val Lys Met Ser Gly Asp Leu Leu Glu Leu Ala Leu Lys Leu
 105 110 115

 ccc cat gtc gac tac atc gag gag gac tcc tct gtc ttt gcc cag agc 483
 Pro His Val Asp Tyr Ile Glu Glu Asp Ser Ser Val Phe Ala Gln Ser
 120 125 130 135

| | |
|---|------|
| atc ccg tgg aac ctg gag cg att acc cct cca ccg tac ccg gcg gat Ile Pro Trp Asn Leu Glu Arg Ile Thr Pro Pro Arg Tyr Arg Ala Asp 140 145 150 | 531 |
| gaa tac cag ccc ccc gac gga ggc agc ctg gtg gag gtg tat ctc cta Glu Tyr Gln Pro Pro Asp Gly Ser Leu Val Glu Val Tyr Leu Leu 155 160 165 | 579 |
| gac acc agc ata cag agt gac cac ccg gaa atc gag ggc agg gtc atg Asp Thr Ser Ile Gln Ser Asp His Arg Glu Ile Glu Gly Arg Val Met 170 175 180 | 627 |
| gtc acc gac ttc gag aat gtg ccc gag gag gac ggg acc cgc ttc cac Val Thr Asp Phe Glu Asn Val Pro Glu Glu Asp Gly Thr Arg Phe His 185 190 195 | 675 |
| aga cag gcc agc aag tgt gac agt cat ggc acc cac ctg gca ggg gtg Arg Gln Ala Ser Lys Cys Asp Ser His Gly Thr His Leu Ala Gly Val 200 205 210 215 | 723 |
| gtc agc ggc cgg gat gcc ggc gtg gcc aag ggt gcc agc atg cgc agc Val Ser Gly Arg Asp Ala Gly Val Ala Lys Gly Ala Ser Met Arg Ser 220 225 230 | 771 |
| ctg cgc gtg ctc aac tgc caa ggg aag ggc acg gtt agc ggc acc ctc Leu Arg Val Leu Asn Cys Gln Gly Lys Gly Thr Val Ser Gly Thr Leu 235 240 245 | 819 |
| ata ggc ctg gag ttt att cgg aaa agc cag ctg gtc cag cct gtg ggg Ile Gly Leu Glu Phe Ile Arg Lys Ser Gln Leu Val Gln Pro Val Gly 250 255 260 | 867 |
| cca ctg gtg ctg ctg ccc ctg gcg ggt ggg tac agc cgc gtc ctc Pro Leu Val Val Leu Leu Pro Leu Ala Gly Gly Tyr Ser Arg Val Leu 265 270 275 | 915 |
| aac gcc gcc tgc cag cgc ctg gcg agg gct ggg gtc gtg ctg gtc acc Asn Ala Ala Cys Gln Arg Leu Ala Arg Ala Gly Val Val Leu Val Thr 280 285 290 295 | 963 |
| gct gcc ggc aac ttc cgg gac gat gcc tgc ctc tac tcc cca gcc tca Ala Ala Gly Asn Phe Arg Asp Asp Ala Cys Leu Tyr Ser Pro Ala Ser 300 305 310 | 1011 |
| gct ccc gag gtc atc aca gtt ggg gcc acc aat gcc cag gac cag ccg Ala Pro Glu Val Ile Thr Val Gly Ala Thr Asn Ala Gln Asp Gln Pro 315 320 325 | 1059 |
| gtg acc ctg ggg act ttg ggg acc aac ttt ggc cgc tgt gtg gac ctc Val Thr Leu Gly Thr Leu Gly Thr Asn Phe Gly Arg Cys Val Asp Leu 330 335 340 | 1107 |

| | |
|---|------|
| ttt gcc cca ggg gag gac atc att ggt gcc tcc agc gac tgc agc acc Phe Ala Pro Gly Glu Asp Ile Ile Gly Ala Ser Ser Asp Cys Ser Thr 345 350 355 | 1155 |
| tgc ttt gtg tca cag agt ggg aca tca cag gct gct gcc cac gtg gct Cys Phe Val Ser Gln Ser Gly Thr Ser Gln Ala Ala Ala His Val Ala 360 365 370 375 | 1203 |
| ggt tgg cag ctg ttt tgc agg act gtg tgg tca gca cac tcg ggg cct Gly Trp Gln Leu Phe Cys Arg Thr Val Trp Ser Ala His Ser Gly Pro 380 385 390 | 1251 |
| aca cgg atg gcc aca gcc atc gcc cgc tgc gcc cca gat gag gag ctg Thr Arg Met Ala Thr Ala Ile Ala Arg Cys Ala Pro Asp Glu Glu Leu 395 400 405 | 1299 |
| ctg agc tgc tcc agt ttc tcc agg agt ggg aag cgg cgg ggc gag cgc Leu Ser Cys Ser Ser Phe Ser Arg Ser Gly Lys Arg Arg Gly Glu Arg 410 415 420 | 1347 |
| atg gag gcc caa ggg ggc aag ctg gtc tgc cgg gcc cac aac gct ttt Met Glu Ala Gln Gly Gly Lys Leu Val Cys Arg Ala His Asn Ala Phe 425 430 435 | 1395 |
| ggg ggt gag ggt gtc tac gcc att gcc agg tgc tgc ctg cta ccc cag Gly Gly Glu Gly Val Tyr Ala Ile Ala Arg Cys Cys Leu Leu Pro Gln 440 445 450 455 | 1443 |
| gcc aac tgc agc gtc cac aca gct cca cca gct gag gcc agc atg ggg Ala Asn Cys Ser Val His Thr Ala Pro Pro Ala Glu Ala Ser Met Gly 460 465 470 | 1491 |
| acc cgt gtc cac tgc cac caa cag ggc cac gtc ctc aca ggc tgc agc Thr Arg Val His Cys His Gln Gln Gly His Val Leu Thr Gly Cys Ser 475 480 485 | 1539 |
| tcc cac tgg gag gtg gag gac ctt ggc acc cac aag ccg cct gtg ctg Ser His Trp Glu Val Glu Asp Leu Gly Thr His Lys Pro Pro Val Leu 490 495 500 | 1587 |
| agg cca cga ggt cag ccc aac cag tgc gtg ggc cac agg gag gcc agc Arg Pro Arg Gly Gln Pro Asn Gln Cys Val Gly His Arg Glu Ala Ser 505 510 515 | 1635 |
| atc cac gct tcc tgc tgc cat gcc cca ggt ctg gaa tgc aaa gtc aag Ile His Ala Ser Cys Cys His Ala Pro Gly Leu Glu Cys Lys Val Lys 520 525 530 535 | 1683 |
| gag cat gga atc ccg gcc cct cag gag cag gtg acc gtg gcc tgc gag Glu His Gly Ile Pro Ala Pro Gln Glu Gln Val Thr Val Ala Cys Glu 540 545 550 | 1731 |

| | |
|---|------|
| gag ggc tgg acc ctg act ggc tgc agt gcc ctc cct ggg acc tcc cac | 1779 |
| Glu Gly Trp Thr Leu Thr Gly Cys Ser Ala Leu Pro Gly Thr Ser His | |
| 555 560 565 | |
| gtc ctg ggg gcc tac gcc gta gac aac acg tgt gta gtc agg agc cg | 1827 |
| Val Leu Gly Ala Tyr Ala Val Asp Asn Thr Cys Val Val Arg Ser Arg | |
| 570 575 580 | |
| gac gtc agc act aca ggc agc acc agc gaa ggg gcc gtg aca gcc gtt | 1875 |
| Asp Val Ser Thr Thr Gly Ser Thr Ser Glu Gly Ala Val Thr Ala Val | |
| 585 590 595 | |
| gcc atc tgc tgc cgg agc cgg cac ctg gcg cag gcc tcc cag gag ctc | 1923 |
| Ala Ile Cys Cys Arg Ser Arg His Leu Ala Gln Ala Ser Gln Glu Leu | |
| 600 605 610 615 | |
| cag tgacagcccc atcccaaggat ggggtgtctgg ggaggggtcaa gg | 1968 |
| Gln | |

<210> 34
 <211> 634
 <212> PRT
 <213> Homo sapiens

<400> 34

Met Gly Thr Val Ser Ser Arg Arg Ser Trp Trp Pro Leu Pro Leu Leu
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 -1 1 5 10

Asp Glu Asp Gly Asp Tyr Glu Glu Leu Val Leu Ala Leu Arg Ser Glu
 15 20 25 30

Glu Asp Gly Leu Ala Glu Ala Pro Glu His Gly Thr Thr Ala Thr Phe
 35 40 45

His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro Gly Thr Tyr Val Val
 50 55 60

Val Leu Lys Glu Glu Thr His Leu Ser Gln Ser Glu Arg Thr Ala Arg
 65 70 75

Arg Leu Gln Ala Gln Ala Ala Arg Arg Gly Tyr Leu Thr Lys Ile Leu
 80 85 90

His Val Phe His Gly Leu Leu Pro Gly Phe Leu Val Lys Met Ser Gly
95 100 105 110

Asp Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile Glu
115 120 125

Glu Asp Ser Ser Val Phe Ala Gln Ser Ile Pro Trp Asn Leu Glu Arg
130 135 140

Ile Thr Pro Pro Arg Tyr Arg Ala Asp Glu Tyr Gln Pro Pro Asp Gly
145 150 155

Gly Ser Leu Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln Ser Asp
160 165 170

His Arg Glu Ile Glu Gly Arg Val Met Val Thr Asp Phe Glu Asn Val
175 180 185 190

Pro Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys Cys Asp
195 200 205

Ser His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp Ala Gly
210 215 220

Val Ala Lys Gly Ala Ser Met Arg Ser Leu Arg Val Leu Asn Cys Gln
225 230 235

Gly Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg
240 245 250

Lys Ser Gln Leu Val Gln Pro Val Gly Pro Leu Val Val Leu Leu Pro
255 260 265 270

Leu Ala Gly Gly Tyr Ser Arg Val Leu Asn Ala Ala Cys Gln Arg Leu
275 280 285

Ala Arg Ala Gly Val Val Leu Val Thr Ala Ala Gly Asn Phe Arg Asp
290 295 300

Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val
305 310 315

Gly Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly
320 325 330

Thr Asn Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Glu Asp Ile
335 340 345 350

Ile Gly Ala Ser Ser Asp Cys Ser Thr Cys Phe Val Ser Gln Ser Gly
355 360 365

Thr Ser Gln Ala Ala Ala His Val Ala Gly Trp Gln Leu Phe Cys Arg
370 375 380

Thr Val Trp Ser Ala His Ser Gly Pro Thr Arg Met Ala Thr Ala Ile
385 390 395

Ala Arg Cys Ala Pro Asp Glu Glu Leu Leu Ser Cys Ser Ser Phe Ser
400 405 410

Arg Ser Gly Lys Arg Arg Gly Glu Arg Met Glu Ala Gln Gly Gly Lys
415 420 425 430

Leu Val Cys Arg Ala His Asn Ala Phe Gly Gly Glu Gly Val Tyr Ala
435 440 445

Ile Ala Arg Cys Cys Leu Leu Pro Gln Ala Asn Cys Ser Val His Thr
450 455 460

Ala Pro Pro Ala Glu Ala Ser Met Gly Thr Arg Val His Cys His Gln
465 470 475

Gln Gly His Val Leu Thr Gly Cys Ser Ser His Trp Glu Val Glu Asp
480 485 490

Leu Gly Thr His Lys Pro Pro Val Leu Arg Pro Arg Gly Gln Pro Asn
495 500 505 510

Gln Cys Val Gly His Arg Glu Ala Ser Ile His Ala Ser Cys Cys His
515 520 525

Ala Pro Gly Leu Glu Cys Lys Val Lys Glu His Gly Ile Pro Ala Pro
530 535 540

Gln Glu Gln Val Thr Val Ala Cys Glu Glu Gly Trp Thr Leu Thr Gly
545 550 555

Cys Ser Ala Leu Pro Gly Thr Ser His Val Leu Gly Ala Tyr Ala Val
560 565 570

Asp Asn Thr Cys Val Val Arg Ser Arg Asp Val Ser Thr Thr Gly Ser
575 580 585 590

Thr Ser Glu Gly Ala Val Thr Ala Val Ala Ile Cys Cys Arg Ser Arg
595 600 605

His Leu Ala Gln Ala Ser Gln Glu Leu Gln
610 615

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Met
-25

gca gag tca ggg ctg gcc atg tgg ccg agc ctg ctg ctc ctg ctg 104
Ala Glu Ser Gly Leu Ala Met Trp Pro Ser Leu Leu Leu Leu Leu
-20 -15 -10

ttg ccg ggg ccc ccg ccc gtc gcc ggc ttg gaa gac gct gcc ttc ccc 152
Leu Pro Gly Pro Pro Pro Val Ala Gly Leu Glu Asp Ala Ala Phe Pro
-5 -1 1 5

| | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|---|-----|
| cac | ctg | ggg | gag | agc | ttg | cag | ccc | ctg | ccc | cg | g | cc | tgt | ccc | ctg | cg | c | 200 |
| His | Leu | Gly | Glu | Ser | Leu | Gln | Pro | Leu | Pro | Arg | Ala | Cys | Pro | Leu | Arg | | | |
| 10 | | | | | | | 15 | | | | | | | 20 | | | | |
| tgc | tcc | tgc | ccc | cga | gtc | gac | act | gtg | gac | tgt | gat | ggc | ttg | gac | ctt | | | 248 |
| Cys | Ser | Cys | Pro | Arg | Val | Asp | Thr | Val | Asp | Cys | Asp | Gly | Leu | Asp | Leu | | | |
| 25 | | | | | 30 | | | | | 35 | | | | | 40 | | | |
| cga | gtg | ttc | ccg | gac | aac | atc | acc | aga | gcc | gct | cag | cac | ctc | tcc | ctg | | | 296 |
| Arg | Val | Phe | Pro | Asp | Asn | Ile | Thr | Arg | Ala | Ala | Gln | His | Leu | Ser | Leu | | | |
| | | | | | 45 | | | | 50 | | | | | 55 | | | | |
| cag | aac | aac | cag | ctc | cag | gaa | ctc | ccc | tac | aat | gag | ctg | tcc | cg | ctc | | | 344 |
| Gln | Asn | Asn | Gln | Leu | Gln | Glu | Leu | Pro | Tyr | Asn | Glu | Leu | Ser | Arg | Leu | | | |
| | | | | | 60 | | | 65 | | | | | 70 | | | | | |
| agt | ggc | ctg | cga | acc | ctc | aac | ctc | cac | aac | ctc | atc | ttc | tcc | gaa | | | | 392 |
| Ser | Gly | Leu | Arg | Thr | Leu | Asn | Leu | His | Asn | Asn | Leu | Ile | Phe | Ser | Glu | | | |
| | | | | | 75 | | | 80 | | | | 85 | | | | | | |
| ggc | ctg | cct | gac | gag | gcc | ttc | gag | tcc | ctc | acc | cag | ctg | cag | cac | ctc | | | 440 |
| Gly | Leu | Pro | Asp | Glu | Ala | Phe | Glu | Ser | Leu | Thr | Gln | Leu | Gln | His | Leu | | | |
| | | | | | 90 | | | 95 | | | | 100 | | | | | | |
| tgc | gtg | gct | cac | aac | aag | ctg | agc | aac | gct | ggc | ctg | ccc | ccc | gac | ggc | | | 488 |
| Cys | Val | Ala | His | Asn | Lys | Leu | Ser | Asn | Ala | Gly | Leu | Pro | Pro | Asp | Ala | | | |
| | | | | | 105 | | | 110 | | 115 | | | | 120 | | | | |
| ttc | cg | gc | tcc | gag | gc | atc | gc | cc | ctc | agc | ctc | tcc | aa | ac | ca | g | | 536 |
| Phe | Arg | Gly | Ser | Glu | Ala | Ile | Ala | Thr | Leu | Ser | Leu | Ser | Asn | Asn | Gln | | | |
| | | | | | 125 | | | | 130 | | | | 135 | | | | | |
| ctc | agc | ta | ctg | ccg | ccc | agc | ctg | ccg | ccc | tca | ctc | gag | cg | ctc | ca | | | 584 |
| Leu | Ser | Tyr | Leu | Pro | Pro | Ser | Leu | Pro | Pro | Ser | Leu | Glu | Arg | Leu | His | | | |
| | | | | | 140 | | | | 145 | | | | 150 | | | | | |
| ctg | cag | aa | at | ctc | atc | tcc | aag | gtg | ccc | cga | gga | gc | ctg | agc | cg | c | | 632 |
| Leu | Gln | Asn | Asn | Leu | Ile | Ser | Lys | Val | Pro | Arg | Gly | Ala | Leu | Ser | Arg | | | |
| | | | | | 155 | | | 160 | | | | 165 | | | | | | |
| cag | act | caa | ctc | cgt | gag | ctc | ta | ctc | cag | ca | ac | cag | ctg | aca | ga | c | | 680 |
| Gln | Thr | Gln | Leu | Arg | Glu | Leu | Tyr | Leu | Gln | His | Asn | Gln | Leu | Thr | Asp | | | |
| | | | | | 170 | | | 175 | | | | 180 | | | | | | |
| agt | ggc | ctg | gat | gc | acc | ac | ttc | agc | aag | ctg | cat | agc | ctt | gaa | ta | | | 728 |
| Ser | Gly | Leu | Asp | Ala | Thr | Thr | Phe | Ser | Lys | Leu | His | Ser | Leu | Glu | Tyr | | | |
| | | | | | 185 | | | | 190 | | | 195 | | | 200 | | | |
| ctg | gat | ctc | tcc | ca | ac | ca | ctg | ac | ca | gtg | ccc | gc | gg | ctg | cc | | | 776 |
| Leu | Asp | Leu | Ser | His | Asn | Gln | Leu | Thr | Thr | Val | Pro | Ala | Gly | Leu | Pro | | | |
| | | | | | 205 | | | | | 210 | | | | 215 | | | | |

| | |
|--|------|
| cg ^g acc ct ^g gct at ^c ct ^g cac ct ^g g ^g c cgc a ^a c cgc at ^c cg ^g cag gt ^g | 824 |
| Arg Thr Leu Ala Ile Leu His Leu Gly Arg Asn Arg Ile Arg Gln Val | |
| 220 225 230 | |
| gag g ^c g gct cg ^g ct ^g cac gg ^g g ^c g cgt g ^g t ct ^g cgc t ^a t tt ^g tt ^g ct ^g | 872 |
| Glu Ala Ala Arg Leu His Gly Ala Arg Gly Leu Arg Tyr Leu Leu Leu | |
| 235 240 245 | |
| cag cac a ^a c cag ct ^g gg ^g ag ^c t ^c a gg ^g ct ^g ccc g ^c c gg ^g gct ct ^g cg ^g | 920 |
| Gln His Asn Gln Leu Gly Ser Ser Gly Leu Pro Ala Gly Ala Leu Arg | |
| 250 255 260 | |
| ccg ct ^g cg ^g gg ^c ct ^g cac ac ^g ct ^g cac ctc t ^a t gg ^c a ^a t gg ^g ct ^g g ^a c | 968 |
| Pro Leu Arg Gly Leu His Thr Leu His Leu Tyr Gly Asn Gly Leu Asp | |
| 265 270 275 280 | |
| cgc gt ^g cct cca g ^c c ct ^g ccc cg ^c cgc ct ^g cgt g ^c c ct ^g gt ^g ct ^g ccc | 1016 |
| Arg Val Pro Pro Ala Leu Pro Arg Arg Leu Arg Ala Leu Val Leu Pro | |
| 285 290 295 | |
| cac a ^a c cac gt ^g g ^c c g ^c g ct ^g g ^g t g ^c c cgt g ^a c ct ^g g ^t c g ^c c a ^c a cc ^g | 1064 |
| His Asn His Val Ala Ala Leu Gly Ala Arg Asp Leu Val Ala Thr Pro | |
| 300 305 310 | |
| gg ^c ct ^g ac ^g gag ctt a ^a c ct ^g g ^c c t ^a t a ^a c cgc ct ^g g ^c c ag ^c g ^c c cgt | 1112 |
| Gly Leu Thr Glu Leu Asn Leu Ala Tyr Asn Arg Leu Ala Ser Ala Arg | |
| 315 320 325 | |
| gt ^g cac cac cg ^g g ^c c tt ^c cgc cg ^g tt ^g cgt g ^c c ct ^g cgc ag ^c ctc g ^a c | 1160 |
| Val His His Arg Ala Phe Arg Arg Leu Arg Ala Leu Arg Ser Leu Asp | |
| 330 335 340 | |
| ct ^g gca gg ^g a ^a t cag cta acc cg ^g ct ^g ccc at ^g g ^c c ct ^g ccc act gg ^c | 1208 |
| Leu Ala Gly Asn Gln Leu Thr Arg Leu Pro Met Gly Leu Pro Thr Gly | |
| 345 350 355 360 | |
| ct ^g cgc acc ct ^g cag ct ^g caa cgc a ^a c cag ct ^g cg ^g at ^g ctc gag ccc | 1256 |
| Leu Arg Thr Leu Gln Leu Gln Arg Asn Gln Leu Arg Met Leu Glu Pro | |
| 365 370 375 | |
| gag cct ct ^g g ^c c gg ^c ct ^g g ^a c caa ct ^g cg ^g gag ctc ag ^c ct ^g g ^c g cac | 1304 |
| Glu Pro Leu Ala Gly Leu Asp Gln Leu Arg Glu Leu Ser Leu Ala His | |
| 380 385 390 | |
| aac cg ^g ctc cg ^g g ^t c g ^c c g ^a c at ^c gg ^g cca g ^c c acc tgg cat gag ctc | 1352 |
| Asn Arg Leu Arg Val Gly Asp Ile Gly Pro Gly Thr Trp His Glu Leu | |
| 395 400 405 | |
| caa g ^c c ctc cag g ^t c agg c ^a c agg ct ^g gtt ag ^c cac act g ^t c ccc agg | 1400 |
| Gln Ala Leu Gln Val Arg His Arg Leu Val Ser His Thr Val Pro Arg | |
| 410 415 420 | |

gcc cct cca tcc ccc tgc ctg ccc tgc cac gtc cca aac att cta gtt 1448
Ala Pro Pro Ser Pro Cys Leu Pro Cys His Val Pro Asn Ile Leu Val
425 430 435 440

agc tgg taaagcaatc agaacaagaa aatgataaga gtgggttaga aggtgataag 1504
Ser Trp

ggc 1507

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<212> PRT
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<400> 36

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Leu Leu Pro Gly Pro Pro Pro Val Ala Gly Leu Glu Asp Ala Ala Phe
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Pro His Leu Gly Glu Ser Leu Gln Pro Leu Pro Arg Ala Cys Pro Leu
10 15 20

Arg Cys Ser Cys Pro Arg Val Asp Thr Val Asp Cys Asp Gly Leu Asp
25 30 35

Leu Arg Val Phe Pro Asp Asn Ile Thr Arg Ala Ala Gln His Leu Ser
40 45 50 55

Leu Gln Asn Asn Gln Leu Gln Glu Leu Pro Tyr Asn Glu Leu Ser Arg
60 65 70

Leu Ser Gly Leu Arg Thr Leu Asn Leu His Asn Asn Leu Ile Phe Ser
75 80 85

Glu Gly Leu Pro Asp Glu Ala Phe Glu Ser Leu Thr Gln Leu Gln His
90 95 100

Leu Cys Val Ala His Asn Lys Leu Ser Asn Ala Gly Leu Pro Pro Asp
105 110 115

Ala Phe Arg Gly Ser Glu Ala Ile Ala Thr Leu Ser Leu Ser Asn Asn
120 125 130 135

Gln Leu Ser Tyr Leu Pro Pro Ser Leu Pro Pro Ser Leu Glu Arg Leu
140 145 150

His Leu Gln Asn Asn Leu Ile Ser Lys Val Pro Arg Gly Ala Leu Ser
155 160 165

Arg Gln Thr Gln Leu Arg Glu Leu Tyr Leu Gln His Asn Gln Leu Thr
170 175 180

Asp Ser Gly Leu Asp Ala Thr Thr Phe Ser Lys Leu His Ser Leu Glu
185 190 195

Tyr Leu Asp Leu Ser His Asn Gln Leu Thr Thr Val Pro Ala Gly Leu
200 205 210 215

Pro Arg Thr Leu Ala Ile Leu His Leu Gly Arg Asn Arg Ile Arg Gln
220 225 230

Val Glu Ala Ala Arg Leu His Gly Ala Arg Gly Leu Arg Tyr Leu Leu
235 240 245

Leu Gln His Asn Gln Leu Gly Ser Ser Gly Leu Pro Ala Gly Ala Leu
250 255 260

Arg Pro Leu Arg Gly Leu His Thr Leu His Leu Tyr Gly Asn Gly Leu
265 270 275

Asp Arg Val Pro Pro Ala Leu Pro Arg Arg Leu Arg Ala Leu Val Leu
280 285 290 295

Pro His Asn His Val Ala Ala Leu Gly Ala Arg Asp Leu Val Ala Thr
300 305 310

Pro Gly Leu Thr Glu Leu Asn Leu Ala Tyr Asn Arg Leu Ala Ser Ala
315 320 325

Arg Val His His Arg Ala Phe Arg Arg Leu Arg Ala Leu Arg Ser Leu
330 335 340

Asp Leu Ala Gly Asn Gln Leu Thr Arg Leu Pro Met Gly Leu Pro Thr
345 350 355

Gly Leu Arg Thr Leu Gln Leu Gln Arg Asn Gln Leu Arg Met Leu Glu
360 365 370 375

Pro Glu Pro Leu Ala Gly Leu Asp Gln Leu Arg Glu Leu Ser Leu Ala
380 385 390

His Asn Arg Leu Arg Val Gly Asp Ile Gly Pro Gly Thr Trp His Glu
395 400 405

Leu Gln Ala Leu Gln Val Arg His Arg Leu Val Ser His Thr Val Pro
410 415 420

Arg Ala Pro Pro Ser Pro Cys Leu Pro Cys His Val Pro Asn Ile Leu
425 430 435

Val Ser Trp
440

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gcgcaaggag aggcccagcg gaagccaagc caccaggccc cccagcgtcc acgcggagca 120
tgaacattga gg atg gcg cgt gcc cgc ggc tcc ccg tgc ccc ccg ctg ccg 171
Met Ala Arg Ala Arg Gly Ser Pro Cys Pro Pro Leu Pro
-35 -30 -25

| | | | |
|--|-----|-----|-----|
| ccc ggt agg atg tcc tgg ccc cac ggg gca ttg ctc ttc ctc tgg ctc Pro Gly Arg Met Ser Trp Pro His Gly Ala Leu Leu Phe Leu Trp Leu | 219 | | |
| -20 | -15 | -10 | |
| ttc tcc cca ccc ctg ggg gcc ggt gga ggt gga gtg gcc gtg acg tct Phe Ser Pro Pro Leu Gly Ala Gly Gly Gly Val Ala Val Thr Ser | 267 | | |
| -5 | -1 | 5 | |
| gcc gcc gga ggg ggc tcc ccg ccg gcc acc tcc tgc ccc gtg gcc tgc Ala Ala Gly Gly Ser Pro Pro Ala Thr Ser Cys Pro Val Ala Cys | 315 | | |
| 10 | 15 | 20 | |
| tcc tgc agc aac cag gcc agc ccg gtg atc tgc aca ccg aga gac ctg Ser Cys Ser Asn Gln Ala Ser Arg Val Ile Cys Thr Arg Arg Asp Leu | 363 | | |
| 25 | 30 | 35 | 40 |
| gcc gag gtc cca gcc agc atc ccg gtc aac acg ccg tac ctg aac ctg Ala Glu Val Pro Ala Ser Ile Pro Val Asn Thr Arg Tyr Leu Asn Leu | 411 | | |
| 45 | 50 | 55 | |
| caa gag aac ggc atc cag gtg atc ccg acg gac acg ttc aag cac ctg Gln Glu Asn Gly Ile Gln Val Ile Arg Thr Asp Thr Phe Lys His Leu | 459 | | |
| 60 | 65 | 70 | |
| cgg cac ctg gag att ctg cag ctg agc aag aac ctg gtg cgc aag atc Arg His Leu Glu Ile Leu Gln Leu Ser Lys Asn Leu Val Arg Lys Ile | 507 | | |
| 75 | 80 | 85 | |
| gag gtg ggc gcc ttc aac ggg ctg ccc agc ctc aac acg ctg gag ctt Glu Val Gly Ala Phe Asn Gly Leu Pro Ser Leu Asn Thr Leu Glu Leu | 555 | | |
| 90 | 95 | 100 | |
| ttt gac aac ccg ctg acc acg gtg ccc acg cag gcc ttc gag tac ctg Phe Asp Asn Arg Leu Thr Thr Val Pro Thr Gln Ala Phe Glu Tyr Leu | 603 | | |
| 105 | 110 | 115 | 120 |
| tcc aag ctg ccg gag ctc tgg ctg ccg aac aac ccc atc gag agc atc Ser Lys Leu Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu Ser Ile | 651 | | |
| 125 | 130 | 135 | |
| ccc tcc tac gcc ttc aac cgc gtg ccc tcg ctg ccg cgc ctg gac ctg Pro Ser Tyr Ala Phe Asn Arg Val Pro Ser Leu Arg Arg Leu Asp Leu | 699 | | |
| 140 | 145 | 150 | |
| ggc gag ctc aag ccg ctg gaa tac atc tcg gag gcg gcc ttc gag ggg Gly Glu Leu Lys Arg Leu Glu Tyr Ile Ser Glu Ala Ala Phe Glu Gly | 747 | | |
| 155 | 160 | 165 | |
| ctg gtc aac ctg cgc tac ctc aac ctg ggc atg tgc aac ctc aag gac Leu Val Asn Leu Arg Tyr Leu Asn Leu Gly Met Cys Asn Leu Lys Asp | 795 | | |
| 170 | 175 | 180 | |

| | |
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| atc ccc aac ctg acg gcc ctg gtg cgc ctg gag gag ctg gag ctg tcg Ile Pro Asn Leu Thr Ala Leu Val Arg Leu Glu Glu Leu Glu Leu Ser 185 190 195 200 | 843 |
| ggc aac cgg ctg gac ctg atc cgc cgg ggc tcc ttc cag ggt ctc acc Gly Asn Arg Leu Asp Leu Ile Arg Pro Gly Ser Phe Gln Gly Leu Thr 205 210 215 | 891 |
| agc ctg cgc aag ctg tgg ctc atg cac gcc cag gta gcc acc atc gag Ser Leu Arg Lys Leu Trp Leu Met His Ala Gln Val Ala Thr Ile Glu 220 225 230 | 939 |
| cgc aac gcc ttc gac gac ctc aag tcg ctg gag gag ctc aac ctg tcc Arg Asn Ala Phe Asp Asp Leu Lys Ser Leu Glu Glu Leu Asn Leu Ser 235 240 245 | 987 |
| cac aac aac ctg atg tcg ctg ccc cac gac ctc ttc acg ccc ctg cac His Asn Asn Leu Met Ser Leu Pro His Asp Leu Phe Thr Pro Leu His 250 255 260 | 1035 |
| cgc ctc gag cgc gtg cac ctc aac cac aac ccc tgg cat tgc aac tgc Arg Leu Glu Arg Val His Leu Asn His Asn Pro Trp His Cys Asn Cys 265 270 275 280 | 1083 |
| gac gtg ctc tgg ctg agc tgg ctc aag gag acg gtg ccc agc aac Asp Val Leu Trp Leu Ser Trp Trp Leu Lys Glu Thr Val Pro Ser Asn 285 290 295 | 1131 |
| acg acg tgc tgc gcc cgc tgt cat gcg ccc gcc ggc ctc aag ggg cgc Thr Thr Cys Cys Ala Arg Cys His Ala Pro Ala Gly Leu Lys Gly Arg 300 305 310 | 1179 |
| tac att ggg gag ctg gac cag tcg cat ttc acc tgc tat gcg ccc gtc Tyr Ile Gly Glu Leu Asp Gln Ser His Phe Thr Cys Tyr Ala Pro Val 315 320 325 | 1227 |
| atc gtg gag ccc acg gac ctc aac gtc acc gag ggc atg gct gcc Ile Val Glu Pro Pro Thr Asp Leu Asn Val Thr Glu Gly Met Ala Ala 330 335 340 | 1275 |
| gag ctc aaa tgc cgc acg ggc acc tcc atg acc tcc gtc aac tgg ctg Glu Leu Lys Cys Arg Thr Gly Thr Ser Met Thr Ser Val Asn Trp Leu 345 350 355 360 | 1323 |
| acg ccc aac ggc acc ctc atg acc cac ggc tcc tac cgc gtg cgc atc Thr Pro Asn Gly Thr Leu Met Thr His Gly Ser Tyr Arg Val Arg Ile 365 370 375 | 1371 |
| tcc gtc ctg cat gac ggc acg ctt aac ttc acc aac gtc acc gtg cag Ser Val Leu His Asp Gly Thr Leu Asn Phe Thr Asn Val Thr Val Gln 380 385 390 | 1419 |

| | |
|---|------|
| gac acg ggc cag tac acg tgc atg gtg acg aac tca gcc ggc aac acc Asp Thr Gly Gln Tyr Thr Cys Met Val Thr Asn Ser Ala Gly Asn Thr 395 400 405 | 1467 |
| acc gcc tcg gcc acg ctc aac gtc tcg gcc gtg gac ccc gtg gcg gcc Thr Ala Ser Ala Thr Leu Asn Val Ser Ala Val Asp Pro Val Ala Ala 410 415 420 | 1515 |
| ggg ggc acc ggc agc ggc ggg ggc ggc cct ggg ggc agt ggt ggt gtt Gly Gly Thr Gly Ser Gly Gly Gly Pro Gly Ser Gly Gly Val 425 430 435 440 | 1563 |
| gga ggg ggc agt ggc ggc tac acc tac ttc acc acg gtg acc gtg gag Gly Gly Ser Gly Gly Tyr Thr Tyr Phe Thr Thr Val Thr Val Glu 445 450 455 | 1611 |
| acc ctg gag acg cag ccc gga gag gag gcc ctg cag ccc cgg ggg acg Thr Leu Glu Thr Gln Pro Gly Glu Ala Leu Gln Pro Arg Gly Thr 460 465 470 | 1659 |
| gag aag gaa ccg cca ggg ccc acg aca gac ggt gtc tgg ggt ggg ggc Glu Lys Glu Pro Pro Gly Pro Thr Thr Asp Gly Val Trp Gly Gly Gly 475 480 485 | 1707 |
| cgg cct ggg gac gcg gcc ggc cct gcc tcg tct tct acc acg gca ccc Arg Pro Gly Asp Ala Ala Gly Pro Ala Ser Ser Thr Thr Ala Pro 490 495 500 | 1755 |
| gcc ccg cgc tcc tcg cgg ccc acg gag aag gcg ttc acg gtg ccc atc Ala Pro Arg Ser Ser Arg Pro Thr Glu Lys Ala Phe Thr Val Pro Ile 505 510 515 520 | 1803 |
| acg gat gtg acg gag aac gcc ctc aag gac ctg gac gac gtc atg aag Thr Asp Val Thr Glu Asn Ala Leu Lys Asp Leu Asp Asp Val Met Lys 525 530 535 | 1851 |
| acc acc aaa atc atc atc ggc tgc ttc gtg gcc atc acg ttc atg gcc Thr Thr Lys Ile Ile Ile Gly Cys Phe Val Ala Ile Thr Phe Met Ala 540 545 550 | 1899 |
| gcg gtg atg ctc gtg gcc ttc tac aag ctg cgc aag cag cac cag ctc Ala Val Met Leu Val Ala Phe Tyr Lys Leu Arg Lys Gln His Gln Leu 555 560 565 | 1947 |
| cac aag cac cac ggg ccc acg cgc acc gtg gag atc atc aac gtg gag His Lys His His Gly Pro Thr Arg Thr Val Glu Ile Ile Asn Val Glu 570 575 580 | 1995 |
| gac gag ctg ccc gcc gcc tgc gtc gtg tcc gtg gcc gcc gcg gcc gcc Asp Glu Leu Pro Ala Ala Ser Ala Val Ser Val Ala Ala Ala Ala 585 590 595 600 | 2043 |

gtg gcc agt ggg ggt ggt gtg ggc ggg gac agc cac ctg gcc ctg ccc 2091
 Val Ala Ser Gly Gly Val Gly Gly Asp Ser His Leu Ala Leu Pro
 605 610 615

gcc ctg gag tgagaccacc tcaaccacca ccactacgtg gctgccgcct 2140
 Ala Leu Glu

tcaaggcgca ctacagcagc aaccccagcg gcggggcgtg cgggggcaaa ggcccgctg 2200
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 <212> PRT
 <213> Homo sapiens

<400> 38

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Met Ser Trp Pro His Gly Ala Leu Leu Phe Leu Trp Leu Phe Ser Pro
 -20 -15 -10

Pro Leu Gly Ala Gly Gly Gly Val Ala Val Thr Ser Ala Ala Gly
 -5 -1 1 5 10

Gly Gly Ser Pro Pro Ala Thr Ser Cys Pro Val Ala Cys Ser Cys Ser
 15 20 25

Asn Gln Ala Ser Arg Val Ile Cys Thr Arg Arg Asp Leu Ala Glu Val
 30 35 40

Pro Ala Ser Ile Pro Val Asn Thr Arg Tyr Leu Asn Leu Gln Glu Asn
 45 50 55

Gly Ile Gln Val Ile Arg Thr Asp Thr Phe Lys His Leu Arg His Leu
 60 65 70 75

Glu Ile Leu Gln Leu Ser Lys Asn Leu Val Arg Lys Ile Glu Val Gly
80 85 90

Ala Phe Asn Gly Leu Pro Ser Leu Asn Thr Leu Glu Leu Phe Asp Asn
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Arg Leu Thr Thr Val Pro Thr Gln Ala Phe Glu Tyr Leu Ser Lys Leu
110 115 120

Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu Ser Ile Pro Ser Tyr
125 130 135

Ala Phe Asn Arg Val Pro Ser Leu Arg Arg Leu Asp Leu Gly Glu Leu
140 145 150 155

Lys Arg Leu Glu Tyr Ile Ser Glu Ala Ala Phe Glu Gly Leu Val Asn
160 165 170

Leu Arg Tyr Leu Asn Leu Gly Met Cys Asn Leu Lys Asp Ile Pro Asn
175 180 185

Leu Thr Ala Leu Val Arg Leu Glu Glu Leu Glu Leu Ser Gly Asn Arg
190 195 200

Leu Asp Leu Ile Arg Pro Gly Ser Phe Gln Gly Leu Thr Ser Leu Arg
205 210 215

Lys Leu Trp Leu Met His Ala Gln Val Ala Thr Ile Glu Arg Asn Ala
220 225 230 235

Phe Asp Asp Leu Lys Ser Leu Glu Glu Leu Asn Leu Ser His Asn Asn
240 245 250

Leu Met Ser Leu Pro His Asp Leu Phe Thr Pro Leu His Arg Leu Glu
255 260 265

Arg Val His Leu Asn His Asn Pro Trp His Cys Asn Cys Asp Val Leu
270 275 280

Trp Leu Ser Trp Trp Leu Lys Glu Thr Val Pro Ser Asn Thr Thr Cys
285 290 295

Cys Ala Arg Cys His Ala Pro Ala Gly Leu Lys Gly Arg Tyr Ile Gly
300 305 310 315

Glu Leu Asp Gln Ser His Phe Thr Cys Tyr Ala Pro Val Ile Val Glu
320 325 330

Pro Pro Thr Asp Leu Asn Val Thr Glu Gly Met Ala Ala Glu Leu Lys
335 340 345

Cys Arg Thr Gly Thr Ser Met Thr Ser Val Asn Trp Leu Thr Pro Asn
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Gly Thr Leu Met Thr His Gly Ser Tyr Arg Val Arg Ile Ser Val Leu
365 370 375

His Asp Gly Thr Leu Asn Phe Thr Asn Val Thr Val Gln Asp Thr Gly
380 385 390 395

Gln Tyr Thr Cys Met Val Thr Asn Ser Ala Gly Asn Thr Thr Ala Ser
400 405 410

Ala Thr Leu Asn Val Ser Ala Val Asp Pro Val Ala Ala Gly Gly Thr
415 420 425

Gly Ser Gly Gly Gly Pro Gly Gly Ser Gly Gly Val Gly Gly Gly
430 435 440

Ser Gly Gly Tyr Thr Tyr Phe Thr Thr Val Thr Val Glu Thr Leu Glu
445 450 455

Thr Gln Pro Gly Glu Ala Leu Gln Pro Arg Gly Thr Glu Lys Glu
460 465 470 475

Pro Pro Gly Pro Thr Thr Asp Gly Val Trp Gly Gly Gly Arg Pro Gly
480 485 490

Asp Ala Ala Gly Pro Ala Ser Ser Ser Thr Thr Ala Pro Ala Pro Arg
495 500 505

Ser Ser Arg Pro Thr Glu Lys Ala Phe Thr Val Pro Ile Thr Asp Val
510 515 520

Thr Glu Asn Ala Leu Lys Asp Leu Asp Asp Val Met Lys Thr Thr Lys
525 530 535

Ile Ile Ile Gly Cys Phe Val Ala Ile Thr Phe Met Ala Ala Val Met
540 545 550 555

Leu Val Ala Phe Tyr Lys Leu Arg Lys Gln His Gln Leu His Lys His
560 565 570

His Gly Pro Thr Arg Thr Val Glu Ile Ile Asn Val Glu Asp Glu Leu
575 580 585

Pro Ala Ala Ser Ala Val Ser Val Ala Ala Ala Ala Val Ala Ser
590 595 600

Gly Gly Gly Val Gly Gly Asp Ser His Leu Ala Leu Pro Ala Leu Glu
605 610 615